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 NEWS  7  DEC 21   IPC search and display fields enhanced in CA/CAplus with the
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 NEWS  8  DEC 23   New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/
                   USPAT2
 NEWS  9  JAN 13   IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
 NEWS 10  JAN 13   New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to
                   INPADOC
 NEWS 11  JAN 17   Pre-1988 INPI data added to MARPAT
 NEWS 12  JAN 17   IPC 8 in the WPI family of databases including WPIFV
 NEWS 13  JAN 30   Saved answer limit increased
 NEWS 14  JAN 31   Monthly current-awareness alert (SDI) frequency
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               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
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FILE 'MEDLINE' ENTERED AT 10:42:38 ON 14 FEB 2006

FILE 'EMBASE' ENTERED AT 10:42:38 ON 14 FEB 2006


FILE 'BIOSIS' ENTERED AT 10:42:38 ON 14 FEB 2006


FILE 'CAPLUS' ENTERED AT 10:42:38 ON 14 FEB 2006


=> s (cnp or c(w)type(w)natriuretic(w)peptide)
L1 6747 (CNP OR C(W) TYPE(W) NATRIURETIC(W) PEPTIDE)

=> s l1 and (skeletal(w)dysplasia or achondroplasia or hypochondroplasia or thanatophoric(w)dysplasia)
L2 32 L1 AND (SKELETAL(W) DYSPLASIA OR ACHONDROPLASIA OR HYPOCHONDROPL ASIA OR THANATOPHORIC(W) DYSPLASIA)

=> dup rem
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PROCESSING COMPLETED FOR L2
L3 16 DUP REM L2 (16 DUPLICATES REMOVED)

=> dis ibib abs l3 1-16

L3 ANSWER 1 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2005173281 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15722353
TITLE: A loss-of-function mutation in natriuretic peptide receptor 2 (Npr2) gene is responsible for disproportionate dwarfism in cn/cn mouse.
AUTHOR: Tsuji Takehito; Kunieda Tetsuo
CORPORATE SOURCE: Graduate School of Natural Science and Technology, Okayama University, 1-1-1, Tsushima-naka, Okayama 700-8530, Japan.. takehito@cc.okayama-u.ac.jp
SOURCE: Journal of biological chemistry, (2005 Apr 8) 280 (14) 14288-92. Electronic Publication: 2005-02-18.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200506
ENTRY DATE: Entered STN: 20050405
Last Updated on STN: 20050622
Entered Medline: 20050621

AB The achondroplastic mouse is a spontaneous mutant characterized by disproportionate dwarfism with short limbs and tail due to disturbed chondrogenesis during endochondral ossification. These abnormal phenotypes are controlled by an autosomal recessive gene (cn). In this study, linkage analysis using 115 affected mice of F2 progeny mapped the cn locus on an approximately 0.8-cM region of chromosome 4, and natriuretic peptide receptor 2 (Npr2) gene was identified as the most potent candidate for the cn mutant in this region. This gene encodes a receptor for **C-type natriuretic peptide** (**CNP**) that positively regulates longitudinal bone growth by producing cGMP in response to **CNP** binding to the extracellular domain. Sequence analyses of the Npr2 gene in cn/cn mice revealed a T to G transversion leading to the amino acid substitution of highly conserved Leu with Arg in the guanylyl cyclase domain. In cultured

chondrocytes of cn/cn mice, stimulus with **CNP** did not significantly increase intracellular cGMP concentration, whereas it increased in +/+ mice. Transfection of the mutant Npr2 gene into COS-7 cells also showed similar results, indicating that the missense mutation of the Npr2 gene in cn/cn mice resulted in disruption of the guanylyl cyclase activity of the receptor. We therefore concluded that the dwarf phenotype of cn/cn mouse is caused by a loss-of-function mutation of the Npr2 gene, and cn/cn mouse will be a useful model to further study the molecular mechanism regulating endochondral ossification by **CNP** /natriuretic peptide receptor B signal.

L3 ANSWER 2 OF 16 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2005576272 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16234329
TITLE: Interaction of fibroblast growth factor and C-natriuretic peptide signaling in regulation of chondrocyte proliferation and extracellular matrix homeostasis.
AUTHOR: Krejci Pavel; Masri Bernard; Fontaine Vincent; Mekikian Pertchoui B; Weis Maryann; Prats Herve; Wilcox William R
CORPORATE SOURCE: Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA.
CONTRACT NUMBER: 5P01-HD22657 (NICHD)
SOURCE: Journal of cell science, (2005 Nov 1) 118 (Pt 21) 5089-100. Electronic Publication: 2005-10-18. Journal code: 0052457. ISSN: 0021-9533.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200512
ENTRY DATE: Entered STN: 20051029
Last Updated on STN: 20051218
Entered Medline: 20051213

AB Overexpression of C-natriuretic peptide (**CNP**) in cartilage partially rescues **achondroplasia** in the mouse. Here, we studied the interaction of fibroblast growth factor (FGF) and **CNP** signaling in chondrocytes. **CNP** antagonized FGF2-induced growth arrest of rat chondrosarcoma (RCS) chondrocytes by inhibition of the Erk mitogen activated protein kinase pathway. This effect of **CNP** was protein kinase G-dependent and was mimicked by the cGMP analog pCPT-cGMP. FGF2-mediated activation of both MEK and Raf-1 but not Ras or FRS2 was abolished by **CNP** demonstrating that **CNP** blocks the Erk pathway at the level of Raf-1. **CNP** also counteracted the FGF2-mediated degradation of RCS extracellular matrix. **CNP** partially antagonized FGF2-induced expression, release and activation of several matrix-remodeling molecules including matrix metalloproteinase 2 (MMP2), MMP3, MMP9, MMP10 and MMP13. In addition, **CNP** compensated for FGF2-mediated matrix loss by upregulation of matrix production independent of its interference with FGF signaling. We conclude that **CNP** utilizes both direct and indirect ways to counteract the effects of FGF signaling in a chondrocyte environment.

L3 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:693139 CAPLUS
DOCUMENT NUMBER: 143:379900
TITLE: Translational research of **CNP** for the treatment of **achondroplasia**
AUTHOR(S): Komatsu, Yasato; Yasoda, Akihiro; Tamura, Naohisa; Nakao, Kazuwa
CORPORATE SOURCE: Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, Kobe-shi, Hyogo, Japan
SOURCE: Saishin Igaku (2005), 60(7), 1594-1599
CODEN: SAIGAK; ISSN: 0370-8241

PUBLISHER: Saishin Igakusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review, on the title study, discussing bone growth stimulatory effects of **C-type natriuretic peptide** ( **CNP**); anal. of **CNP** gene deficient mouse; effectiveness of **CNP** in **achondroplasia**; GC-B gene mutation and guanylate cyclase-B (GC-B) gene knockout mouse development in acromesomelic dysplasia; and **CNP**/GC-B system in endochondral ossification of growth plate cartilages.

L3 ANSWER 4 OF 16 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2005297625 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15869918
TITLE: Complementary antagonistic actions between **C-type natriuretic peptide** and the MAPK pathway through FGFR-3 in ATDC5 cells.
AUTHOR: Ozasa Ami; Komatsu Yasato; Yasoda Akihiro; Miura Masako; Sakuma Yoko; Nakatsuru Yuko; Arai Hiroshi; Itoh Nobuyuki; Nakao Kazuwa
CORPORATE SOURCE: Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho Sakyo-ku, Kyoto 606-8507, Japan.
SOURCE: Bone, (2005 Jun) 36 (6) 1056-64.
Journal code: 8504048. ISSN: 8756-3282.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200511
ENTRY DATE: Entered STN: 20050610
Last Updated on STN: 20051214
Entered Medline: 20051122
AB We previously reported that **C-type natriuretic peptide** (**CNP**) stimulates endochondral ossification and corrects the reduction in body length of **achondroplasia** model mouse with constitutive active fibroblast growth factor receptor 3 (FGFR-3). In order to examine the interaction between **CNP** and FGFR-3, we studied intracellular signaling by using ATDC5 cells, a mouse chondrogenic cell line, and found that FGF2 and FGF18 markedly reduced **CNP**-dependent intracellular cGMP production, and that these effects were attenuated by MAPK inhibitors. Western blot analysis demonstrated that the level of GC-B, a particulate guanylyl cyclase specific for **CNP**, was not changed by treatment with FGFs. Conversely, **CNP** and 8-bromo-cGMP strongly and dose-dependently inhibited the induction of ERK phosphorylation by FGF2 and FGF18 without changing the level of FGFR-3, although they did not affect the phosphorylation of STAT-1. In the organ-cultured fetal mouse tibias, **CNP** and FGF18 counteracted on the longitudinal bone growth, and both the size and number of hypertrophic chondrocytes. The FGF/FGFR-3 pathway is known as the negative regulator of endochondral ossification. We found that FGFs inhibited **CNP**-stimulated cGMP production by disrupting the signaling pathway through GC-B while **CNP** antagonized the activation of the MAPK cascade by FGFs. These results suggest that the **CNP**/GC-B pathway plays an important role in growth plate chondrocytes and constitutes the negative cross talk between FGFs and the activity of MAPK. Our results may explain one of the molecular mechanisms of the growth stimulating action of **CNP** and suggest that activation of the **CNP**/GC-B pathway may be effective as a novel therapeutic strategy for **achondroplasia**.

L3 ANSWER 5 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2004535433 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15506360

TITLE: Current status and future prospects of C-type natriuretic peptide.
AUTHOR: Park Kwijun; Itoh Hiroshi; Nakao Kazuwa
CORPORATE SOURCE: Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine.
SOURCE: Nippon rinsho. Japanese journal of clinical medicine, (2004 Sep) 62 Suppl 9 151-6. Ref: 12
Journal code: 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200501
ENTRY DATE: Entered STN: 20041028
Last Updated on STN: 20050112
Entered Medline: 20050111

L3 ANSWER 6 OF 16 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2004006203 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14702637
TITLE: Overexpression of CNP in chondrocytes rescues achondroplasia through a MAPK-dependent pathway.
AUTHOR: Yasoda Akihiro; Komatsu Yasato; Chusho Hideki; Miyazawa Takashi; Ozasa Ami; Miura Masako; Kurihara Tatsuya; Rogi Tomohiro; Tanaka Shoji; Suda Michio; Tamura Naohisa; Ogawa Yoshihiro; Nakao Kazuwa
CORPORATE SOURCE: Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho Sakyo-ku, Kyoto 606-8507, Japan.
SOURCE: Nature medicine, (2004 Jan) 10 (1) 80-6. Electronic Publication: 2003-12-14.
Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20040106
Last Updated on STN: 20040410
Entered Medline: 20040409

AB Achondroplasia is the most common genetic form of human dwarfism, for which there is presently no effective therapy. C-type natriuretic peptide (CNP) is a newly identified molecule that regulates endochondral bone growth through GC-B, a subtype of particulate guanylyl cyclase. Here we show that targeted overexpression of CNP in chondrocytes counteracts dwarfism in a mouse model of achondroplasia with activated fibroblast growth factor receptor 3 (FGFR-3) in the cartilage. CNP prevented the shortening of achondroplastic bones by correcting the decreased extracellular matrix synthesis in the growth plate through inhibition of the MAPK pathway of FGF signaling. CNP had no effect on the STAT-1 pathway of FGF signaling that mediates the decreased proliferation and the delayed differentiation of achondroplastic chondrocytes. These results demonstrate that activation of the CNP-GC-B system in endochondral bone formation constitutes a new therapeutic strategy for human achondroplasia.

L3 ANSWER 7 OF 16 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2004264627 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15146390
TITLE: Mutations in the transmembrane natriuretic peptide receptor NPR-B impair skeletal growth and cause acromesomelic

dysplasia, type Maroteaux.

AUTHOR: Bartels Cynthia F; Bukulmez Hulya; Padayatti Pius; Rhee David K; van Ravenswaaij-Arts Conny; Pauli Richard M; Mundlos Stefan; Chitayat David; Shih Ling-Yu; Al-Gazali Lihadh I; Kant Sarina; Cole Trevor; Morton Jenny; Cormier-Daire Valerie; Faivre Laurence; Lees Melissa; Kirk Jeremy; Mortier Geert R; Leroy Jules; Zabel Bernhard; Kim Chong Ae; Crow Yanick; Braverman Nancy E; van den Akker Focco; Warman Matthew L

CORPORATE SOURCE: Department of Genetics, Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA.

SOURCE: American journal of human genetics, (2004 Jul) 75 (1) 27-34. Electronic Publication: 2004-05-14. Journal code: 0370475. ISSN: 0002-9297.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200407

ENTRY DATE: Entered STN: 20040528
Last Updated on STN: 20040721
Entered Medline: 20040720

AB The homodimeric transmembrane receptor natriuretic peptide receptor B (NPR-B [also known as guanylate cyclase B, GC-B, and GUC2B]; gene name NPR2) produces cytoplasmic cyclic GMP from GTP on binding its extracellular ligand, **C-type natriuretic peptide** (**CNP**). **CNP** has previously been implicated in the regulation of skeletal growth in transgenic and knockout mice. The autosomal recessive **skeletal dysplasia** known as "acromesomelic dysplasia, type Maroteaux" (AMDM) maps to an interval that contains NPR2. We sequenced DNA from 21 families affected by AMDM and found 4 nonsense mutations, 4 frameshift mutations, 2 splice-site mutations, and 11 missense mutations. Molecular modeling was used to examine the putative protein change brought about by each missense mutation. Three missense mutations were tested in a functional assay and were found to have markedly deficient guanylyl cyclase activity. We also found that obligate carriers of NPR2 mutations have heights that are below the mean for matched controls. We conclude that, although NPR-B is expressed in a number of tissues, its major role is in the regulation of skeletal growth.

L3 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:912938 CAPLUS

DOCUMENT NUMBER: 139:375604

TITLE: Fibroblast growth factor variants with enhanced specificity for receptor subtype and their use for increased cell proliferation

INVENTOR(S): Bogin, Oren; Yayon, Avner

PATENT ASSIGNEE(S): Prochon Biotech Ltd., Israel

SOURCE: PCT Int. Appl., 138 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003094835 | A2 | 20031120 | WO 2003-IL379 | 20030509 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,

TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | | |
|---|---|---|---|---|---|
| CA 2483602 | AA | 20031120 | CA 2003-2483602 | | 20030509 |
| EP 1572080 | A2 | 20050914 | EP 2003-720833 | | 20030509 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | | |
| US 2005148511 | A1 | 20050707 | US 2004-982514 | | 20041105 |
| PRIORITY APPLN. INFO.: | | | IL 2002-149562 | A | 20020509 |
| | | | WO 2003-IL379 | W | 20030509 |

AB The present invention provides fibroblast growth factor (FGF) variants demonstrating enhanced receptor subtype specificity and/or affinity, and specifically, variants of FGF2, FGF4, and FGF9 with amino acid substitutions in the β8-β9 loop and a truncation in either or both the N- or C-terminus. Preferred embodiments include both variants having enhanced activity that act as improved agonists and variants having reduced activity that act as antagonists. Thus, a variant of FGF2 having an asparagine to arginine substitution at position 111 shows essentially unchanged activity towards FGF receptor 3 (FGFR3) and FGFR2 while increasing activity for FGFR1. Introduction of glycine at position Trp-144 of FGF9 abolishes its binding to FGFR1, while retaining significant affinity towards FGFR3 and to a lesser extent, FGFR2. Methods of utilizing preferred FGF variants in preparation of medicaments for the treatment of skeletal disorders including **skeletal dysplasia** and osteoporosis, and enhancing bone fracture healing and cartilage healing processes are provided.

L3 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN

| | |
|---|---|
| ACCESSION NUMBER: | 2003:281946 CAPLUS |
| DOCUMENT NUMBER: | 138:281152 |
| TITLE: | Therapeutic agents for **achondroplasia** |
| INVENTOR(S): | Nakao, Kazuwa |
| PATENT ASSIGNEE(S): | Japan |
| SOURCE: | U.S. Pat. Appl. Publ., 16 pp.<br>CODEN: USXXCO |
| DOCUMENT TYPE: | Patent |
| LANGUAGE: | English |
| FAMILY ACC. NUM. COUNT: | 2 |
| PATENT INFORMATION: | |

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 2003068313 | A1 | 20030410 | US 2002-218109 | | 20020814 |
| US 6743425 | B2 | 20040601 | | | |
| JP 2003104908 | A2 | 20030409 | JP 2001-301586 | | 20010928 |
| JP 2003113116 | A2 | 20030418 | JP 2001-310322 | | 20011005 |
| US 2004198665 | A1 | 20041007 | US 2004-827341 | | 20040420 |
| PRIORITY APPLN. INFO.: | | | JP 2001-301586 | A | 20010928 |
| | | | JP 2001-310322 | A | 20011005 |
| | | | US 2002-218109 | A3 | 20020814 |

AB The present invention aims to provide novel therapeutic agents for **achondroplasia** caused by mutations in FGFR3. Therapeutic agents for treatment of **achondroplasia** caused by the cartilage growth inhibition resulting from mutations in the gene for fibroblast growth factor receptor 3 (FGFR3), comprising a substance activating guanylyl cyclase B (GC-B) as an active ingredient are disclosed. The substance activating GC-B is a derivative of **C-type natriuretic peptide** (**CNP**), such as **CNP**-22 and **CNP**-53. Therapeutic agents for **achondroplasia** can offer an excellent therapy with improved quality of life of patients by relieving burden and pain on the patients as compared with conventional orthopedic surgeries such as artificial hip joint replacement or leg

lengthening. Moreover, **CNP**-transgenic mice generated by a recombinant gene can be used to test their efficacy against **achondroplasia** caused by mutations other than G380R in FGFR3.

L3 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:271678 CAPLUS
DOCUMENT NUMBER: 138:265663
TITLE: Peptides with guanylyl cyclase activity for treatment of **achondroplasia** due to FGFR3 gene mutation
INVENTOR(S): Nakao, Ichikazu
PATENT ASSIGNEE(S): Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 16 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| JP 2003104908 | A2 | 20030409 | JP 2001-301586 | 20010928 |
| BR 2002003172 | A | 20030909 | BR 2002-3172 | 20020813 |
| CA 2398030 | AA | 20030328 | CA 2002-2398030 | 20020814 |
| US 2003068313 | A1 | 20030410 | US 2002-218109 | 20020814 |
| US 6743425 | B2 | 20040601 | | |
| US 2004198665 | A1 | 20041007 | US 2004-827341 | 20040420 |
| PRIORITY APPLN. INFO.: | | | JP 2001-301586 A | 20010928 |
| | | | JP 2001-310322 A | 20011005 |
| | | | US 2002-218109 A3 | 20020814 |

AB Peptides with guanylyl cyclase activity, including **CNP**-22 and **CNP**-53, are claimed for treatment of **achondroplasia** due to FGFR3 gene mutation.

L3 ANSWER 11 OF 16 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2005142658 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15775246
TITLE: The possible novel treatment of **achondroplasia**, **C-type natriuretic peptide** (**CNP**).
AUTHOR: Komatsu Yasato; Yasoda Akihiro; Chusho Hideki; Nakao Kazuwa
CORPORATE SOURCE: Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine.
SOURCE: Clin Calcium, (2003 Dec) 13 (12) 1578-81.
Journal code: 9433326. ISSN: 0917-5857.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: NONMEDLINE; PUBMED-NOT-MEDLINE
ENTRY MONTH: 200505
ENTRY DATE: Entered STN: 20050319
Last Updated on STN: 20050513
Entered Medline: 20050512

AB C-type natiruetic peptide (**CNP**) showed a potent effect on the elongation of the tibial organ culture system. **CNP** also corrected the dwarfing phenotype of the **CNP** knockout mice. These results suggest that **CNP** is the novel promoter of the endochondral ossification, and that **CNP**/GC-B activation is possible target of the treatment of the **achondroplasia**.

L3 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:736053 CAPLUS
DOCUMENT NUMBER: 137:268388
TITLE: Natriuretic peptide composition for treatment of **skeletal dysplasias**

INVENTOR(S): Golembo, Myriam; Yayon, Avner
PATENT ASSIGNEE(S): Prochon Biotech Ltd., Israel
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2002074234 | A2 | 20020926 | WO 2002-IL229 | | 20020320 |
| WO 2002074234 | A3 | 20050106 | | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | | |
| CA 2441815 | AA | 20020926 | CA 2002-2441815 | | 20020320 |
| US 2004138134 | A1 | 20040715 | US 2003-664605 | | 20030915 |
| PRIORITY APPLN. INFO.: | | | IL 2001-142118 | A | 20010320 |
| | | | US 2001-276939P | P | 20010320 |
| | | | WO 2002-IL229 | W | 20020320 |

OTHER SOURCE(S): MARPAT 137:268388

AB The present invention discloses pharmaceutical compns. for the treatment of **skeletal dysplasias**, comprising as an active ingredient at least one natriuretic peptide. Unexpectedly, it has been shown that the natriuretic factors may be effective for bone elongation in situations of abnormal bone growth especially for **achondroplasia**. The effects of the natriuretic peptide may be further enhanced by prolonging its residence time or action at the target site.

L3 ANSWER 13 OF 16 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:431252 BIOSIS
DOCUMENT NUMBER: PREV200300431252
TITLE: **C-type natriuretic peptide** elongates the dwarfing bones in mice model of **achondroplasia** by increasing the extracellular matrix of growth plate chondrocytes.
AUTHOR(S): Yasoda, A. [Reprint Author]; Komatsu, Y. [Reprint Author]; Chusho, H. [Reprint Author]; Ozasa, A. [Reprint Author]; Miyazawa, T. [Reprint Author]; Tamura, N. [Reprint Author]; Ogawa, Y. [Reprint Author]; Nakao, K. [Reprint Author]
CORPORATE SOURCE: Medicine and Clinical Science, Graduate School of Medicine, Kyoto University, Kyoto, Japan
SOURCE: Journal of Bone and Mineral Research, (September 2002) Vol. 17, No. Suppl 1, pp. S173. print.
Meeting Info.: Twenty-Fourth Annual Meeting of the American Society for Bone and Mineral Research. San Antonio, Texas, USA. September 20-24, 2002. American Society for Bone and Mineral Research.
ISSN: 0884-0431 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Sep 2003
Last Updated on STN: 17 Sep 2003

L3 ANSWER 14 OF 16 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2001236549 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11259675
TITLE: Dwarfism and early death in mice lacking C-type natriuretic peptide.
AUTHOR: Chusho H; Tamura N; Ogawa Y; Yasoda A; Suda M; Miyazawa T; Nakamura K; Nakao K; Kurihara T; Komatsu Y; Itoh H; Tanaka K; Saito Y; Katsuki M; Nakao K
CORPORATE SOURCE: Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, Kyoto 606-8507, Japan.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2001 Mar 27) 98 (7) 4016-21. Electronic Publication: 2001-03-20. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20030105
Entered Medline: 20010503

AB Longitudinal bone growth is determined by endochondral ossification that occurs as chondrocytes in the cartilaginous growth plate undergo proliferation, hypertrophy, cell death, and osteoblastic replacement. The natriuretic peptide family consists of three structurally related endogenous ligands, atrial, brain, and **C-type natriuretic peptides** (ANP, BNP, and **CNP**), and is thought to be involved in a variety of homeostatic processes. To investigate the physiological significance of **CNP** in vivo, we generated mice with targeted disruption of **CNP** (Nppc(-/-) mice). The Nppc(-/-) mice show severe dwarfism as a result of impaired endochondral ossification. They are all viable perinatally, but less than half can survive during postnatal development. The skeletal phenotypes are histologically similar to those seen in patients with **achondroplasia**, the most common genetic form of human dwarfism. Targeted expression of **CNP** in the growth plate chondrocytes can rescue the skeletal defect of Nppc(-/-) mice and allow their prolonged survival. This study demonstrates that **CNP** acts locally as a positive regulator of endochondral ossification in vivo and suggests its pathophysiological and therapeutic implication in some forms of **skeletal dysplasia**.

L3 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:114423 CAPLUS
DOCUMENT NUMBER: 136:380196
TITLE: Enhanced endochondral ossification by natriuretic peptides
AUTHOR(S): Chusho, Hideki; Ogawa, Yoshihiro; Tamura, Naohisa; Komatsu, Yasato; Nakao, Kazuwa
CORPORATE SOURCE: Graduate School of Medicine, Kyoto University, Japan
SOURCE: Bone (Osaka, Japan) (2001), 15(6), 669-673
CODEN: BONEFN; ISSN: 0914-7047
PUBLISHER: Medikaru Rebyusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review, on roles of **C-type natriuretic peptides** (ANP, BNP, and **CNP**) in regulation of endochondral ossification. **CNP** may act as a local pos. regulator of endochondral ossification and may also have pathophysiol. and therapeutic implication in dwarfism and other forms of **skeletal dysplasia**.

L3 ANSWER 16 OF 16 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:561817 BIOSIS
DOCUMENT NUMBER: PREV200100561817
TITLE: Targeted overexpression of **C-type natriuretic peptide** in the growth plate rescued dwarfism of the transgenic mice of constitutive active FGF receptor 3.
AUTHOR(S): Yasoda, A. [Reprint author]; Komatsu, Y. [Reprint author]; Chusho, H. [Reprint author]; Miyazawa, T. [Reprint author]; Miura, M. [Reprint author]; Suda, M. [Reprint author]; Tanaka, K. [Reprint author]; Ogawa, Y. [Reprint author]; Ornitz, D. M.; Nakao, K. [Reprint author]
CORPORATE SOURCE: Medicine and Clinical Science, Kyoto University Graduate School of Medicine, Kyoto, Japan
SOURCE: Journal of Bone and Mineral Research, (September, 2001) Vol. 16, No. Suppl. 1, pp. S188. print.
Meeting Info.: Twenty-Third Annual Meeting of the American Society for Bone and Mineral Research. Phoenix, Arizona, USA. October 12-16, 2001.
CODEN: JBMREJ. ISSN: 0884-0431.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Dec 2001
Last Updated on STN: 25 Feb 2002

=> dis his

(FILE 'HOME' ENTERED AT 10:42:25 ON 14 FEB 2006)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 10:42:38 ON 14 FEB 2006
L1 6747 S (CNP OR C(W)TYPE(W)NATRIURETIC(W)PEPTIDE)
L2 32 S L1 AND (SKELETAL(W)DYSPLASIA OR ACHONDROPLASIA OR HYPOCHONDRO
L3 16 DUP REM L2 (16 DUPLICATES REMOVED)

=> s l1 and (gh or growth(w)hormone)
L4 45 L1 AND (GH OR GROWTH(W) HORMONE)

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 21 DUP REM L4 (24 DUPLICATES REMOVED)

=> dis ibib abs l4 1-21

L4 ANSWER 1 OF 45 MEDLINE on STN
ACCESSION NUMBER: 2003094867 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12606276
TITLE: Effects of angiotensin II and natriuretic peptides of the eel on prolactin and **growth hormone** release in the tilapia, Oreochromis mossambicus.
AUTHOR: Eckert Steve M; Hirano Tetsuya; Leedom Thomas A; Takei Yoshio; Gordon Grau E
CORPORATE SOURCE: Department of Zoology and Hawaii Institute of Marine Biology, University of Hawaii, PO Box 1346, Coconut Island, Kaneohe, HI 96744, USA.
SOURCE: General and comparative endocrinology, (2003 Feb 15) 130 (3) 333-9.
Journal code: 0370735. ISSN: 0016-6480.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030228
Last Updated on STN: 20031024
Entered Medline: 20031023

AB The effects of angiotensin II (ANG II) and natriuretic peptides (NPs) of the eel (ANP, atrial natriuretic peptide; **CNP**, **C-type natriuretic peptide**; and VNP, ventricular natriuretic peptide) on prolactin (PRL(188) and PRL(177)) and **growth hormone** (**GH**) release from the organ-cultured tilapia pituitary were examined. Eel ANG II at concentrations greater than 1 nM stimulated the release of PRL(188) and PRL(177) in a dose-related manner during the first hour of incubation. Significant stimulation by 100 nM ANG II on PRL(177) release was observed until 4h of incubation, and on PRL(188) release until 12 h. No effect of ANG II was seen on **GH** release. None of the NPs altered the release of PRLs at any time point. On the other hand, eel VNP at concentrations greater than 1 nM stimulated **GH** release in a dose-related manner after 4 h, and significant stimulation was observed until 48 h. Eel **CNP** was less effective than eel VNP; significant stimulation of **GH** release was observed at 1 and 10 nM during 24-48 h of incubation. No significant effect of eel ANP on **GH** release was seen at any concentration. ANG II had no effect on **GH** release at any time point. There was no change in mRNA levels of PRLs or **GH** in the pituitaries incubated with ANG II for 8 h or those incubated with the NPs for 48 h. These results indicate rapid and short-lasting stimulation by ANG II on PRL release and slow and long-lasting stimulation by VNP and **CNP** on **GH** release from the tilapia pituitary.


L4 ANSWER 2 OF 45 MEDLINE on STN
ACCESSION NUMBER: 2002408895 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12163347
TITLE: Comparison of vasodilators in human internal mammary artery: ghrelin is a potent physiological antagonist of endothelin-1.
AUTHOR: Wiley Katherine E; Davenport Anthony P
CORPORATE SOURCE: Clinical Pharmacology Unit, University of Cambridge, Level 6, Centre for Clinical Investigation, Box 110, Addenbrooke's Hospital, UK.. kew29@hermes.cam.ac.uk
SOURCE: British journal of pharmacology, (2002 Aug) 136 (8) 1146-52.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20020807
Last Updated on STN: 20030429
Entered Medline: 20030428

AB 1 The potential vasodilator function of the peptide ghrelin, recently identified as the endogenous ligand of the **growth hormone** secretagogue orphan receptor (**GHS**-R), was investigated in human endothelium-denuded internal mammary artery. The peptide endothelin-1 (ET-1) is a potent and long-lasting vasoconstrictor. Comparisons were made with established and putative endogenous vasodilators to determine if any could reverse ET-1-induced vasoconstriction in this vessel. 2 Ghrelin (0.1-300 nM) potently dilated 10 nM ET-1-induced constrictions (pD(2) 8.39+/-0.29; E(MAX) 63+/-5.6%; n=9/14, responders/total). 3 ANP (pD(2) 7.75+/-0.14; E(MAX) 106+/-2.0; n=5/5) and CGRP (pD(2) 8.08+/-0.17; E(MAX) 76+/-15% n=5/6) both produced complete reversal of the constrictor response to ET-1 (E(MAX) not significantly different from 100%, P>0.05 one-sample t-test). 4 The

following caused partial reversal of the ET-1 response: Adrenomedullin (n=9/9) and two peptides derived from proadrenomedullin, PAMP-12 (n=6/7) and PAMP-20 (n=9/9) (pD(2) values 7.63+/-0.28, 7.97+/-0.23 and 8.51+/-0.29; E(MAX) 58+/-7.3, 54+/-10 and 51+/-7.8% respectively). Unexpectedly, amylin was only 2 fold less potent than CGRP, although there was less than 50% reversal of the ET-1 constriction (pD(2) 7.86+/-0.30; E(MAX) 41+/-5.4%; n=7/9). **CNP** (n=6/6) also partially reversed constrictions to ET-1 (E(MAX) 53+/-6.3; pD(2) 8.07+/-0.38). 5 BNP (n=4/5) and PGI(2) (n=6/8) were weak vasodilators, since concentration-response curves failed to reach a maximum within the range tested. PGE(2) caused a small dilatation in some vessels (E(MAX) 17+/-2.1%; pD(2) 8.63+/-0.36; n=4/8). 6 We have demonstrated ghrelin to be an effective, endothelium-independent vasodilator of the long-lasting constrictor ET-1 in human arteries producing responses similar to those of adrenomedullin (P>0.05, ANOVA). British Journal of Pharmacology (2002) 136, 1146-1152

L4 ANSWER 3 OF 45 MEDLINE on STN
ACCESSION NUMBER: 2000397230 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10856898
TITLE: **C-type natriuretic peptide** (**CNP**) effects in anterior pituitary cell lines: evidence for homologous desensitisation of **CNP**-stimulated cGMP accumulation in alpha T3-1 gonadotroph-derived cells.
AUTHOR: Fowkes R C; Forrest-Owen W; McArdle C A
CORPORATE SOURCE: Division of Medicine, Department of Hospital Medicine, University of Bristol, Bristol Royal Infirmary, Marlborough Street, Bristol BS2 8HW, UK.. r.c.fowlkes@mds.qmw.ac.uk
SOURCE: Journal of endocrinology, (2000 Jul) 166 (1) 195-203. Journal code: 0375363. ISSN: 0022-0795.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000824
Last Updated on STN: 20000824
Entered Medline: 20000817

AB **C-type natriuretic peptide** (**CNP**), the third member of the natriuretic peptide family, has been found at its highest tissue concentrations in the anterior pituitary, where it is localised in gonadotrophs. Its specific guanylyl cyclase-containing receptor, GC-B, is also expressed on several anterior pituitary cell types, and **CNP** potently stimulates cGMP accumulation in rat pituitary cell cultures and pituitary cell lines. The mouse gonadotroph-derived alpha T3-1 cell line has been shown to express **CNP** as well as GC-B (but not GC-A) receptors, suggesting that **CNP** may well be an autocrine regulator of gonadotrophs. Comparing effects of three natriuretic peptides (atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and **CNP**) on cGMP accumulation in four pituitary cell lines (alpha T3-1, TtT-GF, AtT-20 and GH (3)) we find that **CNP** is most potent and effective in alpha T3-1 cells. In these cells, **CNP**-stimulated cGMP accumulation was found to desensitise during a 30 min exposure to **CNP**. Pretreatment with **CNP** for up to 6 h also caused a significant reduction in the ability of **CNP** to subsequently stimulate cGMP accumulation. This effect was receptor specific, because pretreatment with sodium nitroprusside (an activator of nitric oxide-sensitive guanylyl cyclase), or with ANP or BNP, did not cause desensitisation of **CNP** -stimulated cGMP accumulation. Protein kinase C activation with phorbol esters also inhibited **CNP**-stimulated cGMP accumulation and such inhibition was also seen in cells desensitised by pretreatment with **CNP**. Thus it appears that the endogenous GC-B receptors of alpha T3-1 cells are subject to both homologous and heterologous

desensitisation, that the mechanisms underlying these forms of desensitisation are distinct, and that cGMP elevation alone is insufficient to desensitise GC-B receptors.

L4 ANSWER 4 OF 45 MEDLINE on STN
ACCESSION NUMBER: 96024586 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7575564
TITLE: Cyclic GMP stimulates **growth hormone** release in rat anterior pituitary cells.
AUTHOR: Hartt D J; Ogiwara T; Ho A K; Chik C L
CORPORATE SOURCE: Department of Medicine, Faculty of Medicine, University of Alberta, Edmonton, Canada.
SOURCE: Biochemical and biophysical research communications, (1995 Sep 25) 214 (3) 918-26.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19990129
Entered Medline: 19951102

AB In this study, the role of cGMP on **growth hormone** (**GH**) release was examined using a static monolayer culture prepared from dispersed rat anterior pituitary cells. Treatment with 8-bromo-cGMP (1 microM to 1 mM) stimulated **GH** release up to 3.8-fold in a concentration-dependent manner. Elevating cGMP with nitroprusside or the **C-type natriuretic peptide** was also effective in stimulating **GH** release. The increase in **GH** release by cGMP-elevating agents occurred without a concomitant increase in cAMP. Unlike cAMP which increased intracellular Ca2+ concentration, 8-bromo-cGMP caused a small reduction in intracellular Ca2+ concentration. Taken together, these results indicate that i) cGMP appears to be another mechanism that regulates **GH** release, ii) activation of cytosolic or membranous guanylyl cyclase is equally effective in stimulating **GH** release; and iii) the cGMP-induced **GH** release appears to be through a mechanism distinct from that of cAMP.

L4 ANSWER 5 OF 45 MEDLINE on STN
ACCESSION NUMBER: 94291663 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8020502
TITLE: **C-type natriuretic peptide** stimulates secretion of **growth hormone** from rat-pituitary-derived GH3 cells via a cyclic-GMP-mediated pathway.
AUTHOR: Shimekake Y; Ohta S; Nagata K
CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi & Co. Ltd., Osaka, Japan.
SOURCE: European journal of biochemistry / FEBS, (1994 Jun 1) 222 (2) 645-50.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940815
Last Updated on STN: 19990129
Entered Medline: 19940804

AB Although **C-type natriuretic peptide** (**CNP**) has been shown to exist at the highest concentration in the anterior pituitary in rat tissues, its physiological role(s) there is (are) not clear. In this study, we report a novel function of **CNP**

examined with anterior pituitary-derived cell lines, GH3 and AtT20/D16v-F2. Both **CNP** and atrial natriuretic peptide (ANP) increased cellular cGMP levels in both cell lines in dose-dependent manners. **CNP**, but not ANP, stimulated **growth hormone** (**GH**) release from GH3 cells. In contrast, neither ANP nor **CNP** had any significant effect on the corticotropin release from AtT20/D16v-F2 cells. An activator for cGMP-dependent protein kinase (cGK), dibutyryl cGMP, mimicked the stimulation of **GH** release from GH3 cells by **CNP**. Constitutive **GH** release from GH3 cells was greatly diminished in the presence of inhibitors for cAMP-dependent protein kinase, while stimulative **GH** release by **CNP** was not affected. However, inhibitors which can block cGK almost completely diminished the stimulative effect of **CNP**. An inhibitor for protein kinase C did not show any effect on either constitutive or **CNP** -stimulative **GH** release. Our observations indicate that the stimulation of **GH** release from GH3 cells by **CNP** is mediated mainly by the cGK signal-transduction pathway, not by cAMP-dependent protein kinase or protein kinase C, through a **CNP** -specific receptor (possibly ANP-B receptor). Thus, **CNP** may act as a local modulator in the anterior pituitary.

L4 ANSWER 6 OF 45 MEDLINE on STN
ACCESSION NUMBER: 93309441 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8321215
TITLE: Cell-type-specific function of the **C-type natriuretic peptide** gene promoter in rat anterior pituitary-derived cultured cell lines.
AUTHOR: Ohta S; Shimekake Y; Nagata K
CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka 553, Japan.
SOURCE: Molecular and cellular biology, (1993 Jul) 13 (7) 4077-86. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930813
Last Updated on STN: 19990129
Entered Medline: 19930730

AB The promoter function of the human **C-type natriuretic peptide** (**CNP**) gene in various cultured cells was examined by transient transfection assays. The **CNP** promoter functioned very effectively in GH3 cells, which originated from the **growth hormone**-producing tumor of the rat anterior pituitary and somatomammotroph phenotype, but functioned much less effectively in GH1 cells, another type of rat pituitary-derived cell with a somatotroph phenotype, and rat primary cardiocytes. The **CNP** promoter did not function at all in other cells, including AtT20 cells of murine pituitary corticotroph origin. Functional analyses of the deleted promoters with various 5' deletion breakpoints revealed the existence of at least two negative and one positive regulatory regions. Within the positive regulatory region (positions -54 to -19), which conferred 90% of the promoter activity in GH3 cells, two equipotent GC-rich cis elements (positions -49 to -45 and -40 to -35) were identified. Both sites shared half of the promoter activity and binding properties to the nuclear protein in GH3 cells. Rat anterior pituitary tissue contained the binding protein of the identified cis element, which was identical or similar to that of GH3 cells. With Southwestern (DNA-protein) analysis, a 70-kDa specific binding protein distinct from known factors such as SP-1, AP-2, and Pit-1 was identified in the nuclear extract of GH3 cells.

L4 ANSWER 7 OF 45 MEDLINE on STN
ACCESSION NUMBER: 89055051 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3193044
TITLE: Effect of **growth hormone** on growth and myelination in the neonatal hypothyroid rat.
AUTHOR: King R A; Smith R M; Meller D J; Dahlenburg G W; Lineham J D
CORPORATE SOURCE: CSIRO (Australia), Division of Human Nutrition, Adelaide, South Australia.
SOURCE: Journal of endocrinology, (1988 Oct) 119 (1) 117-25.
Journal code: 0375363. ISSN: 0022-0795.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198901
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19890106

AB The possible involvement of a deficit of **GH** and insulin-like growth factor-I (somatomedin C) (IGF-I/SMC) in mediating the effects of propylthiouracil (PTU)-induced hypothyroidism on body and skeletal growth and myelination was studied in the neonatal rat. Myelination (as assessed by 2',3'-cyclic nucleotide 3'-phosphohydrolase (**CNP**) activity), skeletal growth (as assessed by tail length) and body weight of pups from PTU-treated mothers were significantly retarded compared with normal animals or euthyroid controls. At 20 days after birth, plasma **GH** in hypothyroid animals was undetectable (less than 10 micrograms/l), pituitary **GH** content was 1.2% of control, and plasma, liver and kidney IGF-I/SMC concentrations were 63, 68 and 50% of control values respectively. **CNP** activity in hypothyroid brain was 52% of normal controls but the concentration of IGF-I/SMC was 113-154% of control. Treatment of hypothyroid animals from day 1 with **GH** (10 mg/kg body weight per day) restored liver and plasma IGF-I/SMC concentrations at 20 days to values above those of normal animals and euthyroid controls. The concentration of IGF-I/SMC was also significantly (P less than 0.001) restored in hypothyroid kidney (79% of normal), but the concentration in brain was unaffected. These observations provide evidence that the **GH** treatment employed in the present experiments was adequate to restore the deficit. **GH** treatment had no significant effect on tail length or **CNP** activity, and only a small (4-24%) effect on body weight at 20 days. Only thyroxine was able fully to restore body weight and substantially restore tail length and **CNP** activity.(ABSTRACT TRUNCATED AT 250 WORDS)

L4 ANSWER 8 OF 45 MEDLINE on STN
ACCESSION NUMBER: 86001732 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2412655
TITLE: Epidermal growth factor and bovine **growth hormone** stimulate differentiation and myelination of brain cell aggregates in culture.
AUTHOR: Almazan G; Honegger P; Matthieu J M; Guentert-Lauber B
SOURCE: Brain research, (1985 Aug) 353 (2) 257-64.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198510
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 20000303
Entered Medline: 19851029

AB Bovine **growth hormone** (bGH) and epidermal growth factor (EGF) increased the activity of ornithine decarboxylase (ODC) in

brain cell aggregates cultured in a serum-free chemically defined medium. ODC is considered as a marker of cell growth and differentiation. The effect of bGH and EGF on myelination was investigated by measuring two myelin markers, 2',3'-cyclic nucleotide 3'-phosphodiesterase (**CNP** ) and myelin basic protein (MBP). EGF treatment at days 2 and 5 caused a dose-dependent increase of both myelin markers at culture day 12. This increase could still be observed at culture day 19, indicating a prolonged action of EGF. The continual presence of bGH in the culture medium produced a large accumulation of MBP at day 19. This effect was dose-dependent and required the presence of triiodothyronine (T3). In contrast, the effect of bGH on **CNP** activity did not require the presence of T3. This is the first report showing a direct effect of bGH on CNS myelination in vitro and of EGF on both MBP accumulation and ODC activity.

L4 ANSWER 9 OF 45 MEDLINE on STN
ACCESSION NUMBER: 83163218 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6834036
TITLE: Cerebroside and sulfatide biosynthesis in the brain of Snell dwarf mouse: effects of thyroxine and **growth hormone** in the early postnatal period.
AUTHOR: Sarlieve L L; Bouchon R; Koehl C; Neskovic N M
SOURCE: Journal of neurochemistry, (1983 Apr) 40 (4) 1058-62. Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198305
ENTRY DATE: Entered STN: 19900318
Last Updated on STN: 19990129
Entered Medline: 19830505

AB Snell dwarf mice (dw/dw) and normal mice (+/?) were injected with thyroxine (T4) (1 microgram/animal, four injections) and **growth hormone** (**GH**) (20 micrograms/animal, four injections) from the 5th to the 15th day of life. In the untreated dw/dw mouse brain, the specific activities of UDP-galactose:ceramide galactosyltransferase (CGalT), PAPS:cerebroside sulfotransferase (CST), and 2', 3'-cyclic nucleotide 3'-phosphohydrolase (**CNP**) were decreased by 28, 25, and 37%, respectively, compared with the control untreated +/? mice. The major effect of T4 was an increase of the brain **CNP** in the +/? mice (+40%) and dw/dw mice (+111%). The treatment with T4 also brought to normal the level of CGalT in dw/dw brain; a somewhat less marked effect on CST was observed. The treatment with **GH** had a great stimulatory effect on **CNP**: the specific activity of this enzyme increased by 40 and 69% in +/? and dw/dw mouse brain, respectively. On the contrary, no effect of **GH** on the CGalT activity was observed in this study. Our results suggest that T4 and **GH** may have both independent and complementary actions on the myelin-associated enzymes during the early postnatal period of brain development.

L4 ANSWER 10 OF 45 EMBASE 
ACCESSION NUMBER: 2003079151 EMBASE
TITLE: Effects of angiotensin II and natriuretic peptides of the eel on prolactin and **growth hormone** release in the tilapia, Oreochromis mossambicus.
AUTHOR: Eckert S.M.; Hirano T.; Leedom T.A.; Takei Y.; Grau E.G.
CORPORATE SOURCE: E.G. Grau, Department of Zoology, Hawaii Institute of Marine Biology, University of Hawaii, P.O. Box 1346, Kaneohe, HI 96744, United States. grau@hawaii.edu
SOURCE: General and Comparative Endocrinology, (15 Feb 2003) Vol. 130, No. 3, pp. 333-339. .
Refs: 41

ISSN: 0016-6480 CODEN: GCENA5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030306
Last Updated on STN: 20030306

AB The effects of angiotensin II (ANG II) and natriuretic peptides (NPs) of the eel (ANP, atrial natriuretic peptide; **CNP**, **C-type natriuretic peptide**; and VNP, ventricular natriuretic peptide) on prolactin (PRL(188) and PRL(177)) and **growth hormone** (**GH**) release from the organ-cultured tilapia pituitary were examined. Eel ANG II at concentrations greater than 1nM stimulated the release of PRL(188) and PRL(177) in a dose-related manner during the first hour of incubation. Significant stimulation by 100nM ANG II on PRL(177) release was observed until 4h of incubation, and on PRL(188) release until 12h. No effect of ANG II was seen on **GH** release. None of the NPs altered the release of PRLs at any time point. On the other hand, eel VNP at concentrations greater than 1nM stimulated **GH** release in a dose-related manner after 4h, and significant stimulation was observed until 48h. Eel **CNP** was less effective than eel VNP; significant stimulation of **GH** release was observed at 1 and 10nM during 24-48h of incubation. No significant effect of eel ANP on **GH** release was seen at any concentration. ANG II had no effect on **GH** release at any time point. There was no change in mRNA levels of PRLs or **GH** in the pituitaries incubated with ANG II for 8h or those incubated with the NPs for 48h. These results indicate rapid and short-lasting stimulation by ANG II on PRL release and slow and long-lasting stimulation by VNP and **CNP** on **GH** release from the tilapia pituitary. 

L4 ANSWER 11 OF 45 EMBASE 
ACCESSION NUMBER: 2002314685 EMBASE
TITLE: Comparison of vasodilators in human internal mammary artery: Ghrelin is a potent physiological antagonist of endothelin-1.
AUTHOR: Wiley K.E.; Davenport A.P.
CORPORATE SOURCE: K.E. Wiley, Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QQ, United Kingdom. kew29@hermes.cam.ac.uk
SOURCE: British Journal of Pharmacology, (2002) Vol. 136, No. 8, pp. 1146-1152. .
Refs: 50
ISSN: 0007-1188 CODEN: BJPCBM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20020919
Last Updated on STN: 20020919

AB 1. The potential vasodilator function of the peptide ghrelin, recently identified as the endogenous ligand of the **growth hormone** secretagogue orphan receptor (**GHS**-R), was investigated in human endothelium-denuded internal mammary artery. The peptide endothelin-1 (ET-1) is a potent and long-lasting vasoconstrictor. Comparisons were made with established and putative endogenous

vasodilators to determine if any could reverse ET-1-induced vasoconstriction in this vessel. 2. Ghrelin (0.1-300 nM) potently dilated 10 nM ET-1-induced constrictions (pD(2) 8.39±0.29; E(MAX) 63 ± 5.6%; n = 9/14, responders/total). 3. ANP (pD(2) 7.75 ± 0.14; E(MAX) 106 ± 2.0; n = 5/5) and CGRP (pD(2) 8.08 ± 0.17; E(MAX) 76 ± 15% n = 5/6) both produced complete reversal of the constrictor response to ET-1 (E(MAX) not significantly different from 100%, P > 0.05 one-sample t-test). 4. The following caused partial reversal of the ET-1 response: Adrenomedullin (n = 9/9) and two peptides derived from proadrenomedullin, PAMP-12 (n = 6/7) and PAMP-20 (n = 9/9) (pD(2) values 7.63 ± 0.28, 7.97 ± 0.23 and 8.51 ± 0.29; E(MAX) 58 ± 7.3, 54 ± 10 and 51 ± 7.8% respectively). Unexpectedly, amylin was only 2 fold less potent than CGRP, although there was less than 50% reversal of the ET-1 constriction (pD(2) 7.86 ± 0.30; E(MAX) 41 ± 5.4%; n = 7/9). **CNP** (n = 6/6) also partially reversed constrictions to ET-1 (E(MAX) 53 ± 6.3; pD(2) 8.07 ± 0.38). 5. BNP (n = 4/5) and PGI(2) (n = 6/8) were weak vasodilators, since concentration-response curves failed to reach a maximum within the range tested. PGE(2) caused a small dilatation in some vessels (E(MAX) 17 ± 2.1%; pD(2) 8.63 ± 0.36; n = 4/8). 6. We have demonstrated ghrelin to be an effective, endothelium-independent vasodilator of the long-lasting constrictor ET-1 in human arteries producing responses similar to those of adrenomedullin (P > 0.05, ANOVA).

L4 ANSWER 12 OF 45 EMBASE 

ACCESSION NUMBER: 97029822 EMBASE
DOCUMENT NUMBER: 1997029822
TITLE: **C-type natriuretic peptide**: Regulatory mechanism of gene expression and novel biological function.
AUTHOR: Nagata K.; Shimekake Y.; Ohta S.
CORPORATE SOURCE: Y. Shimekake, DNAVEC Research Inc., 25-11 Kannondai 1-Chome, Tsukuba-shi, Ibaragi 305, Japan
SOURCE: Annual Report of Shionogi Research Laboratory, (1996) No. 46, pp. 24-47. .
Refs: 80
ISSN: 0559-8680 CODEN: SKNEA7
COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 970218
Last Updated on STN: 970218

AB The promoter of human **C-type natriuretic peptide** (**CNP**) gene functions very effectively in rat anterior pituitary-derived GH3 cells. Extensive functional analysis of **CNP** promoter revealed the existence of a positive regulatory region consisting of two GC-rich sequence elements which fire equipotent in DNA binding specificity and transcriptional activity and confer 90% of the promoter function. The promoter function of the positive regulatory region was stimulated by transforming growth factor (TGF) -β or other cytokines. The transcription factor affecting the GC-rich element was cloned by Southwestern screening, and identified as TSC-22 which was originally isolated from mouse osteoblastoma cells as a TGF-β stimulated clone. TSC-22 stimulated the **CNP** promoter function when it was transiently expressed in GH3 as well as in human aortic endothelial cells (HAEC). TSC-22 gene expression in GH3 and HAEC was stimulated by cytokines including TGF- β, in correlation with the **CNP** mRNA increase, suggesting that TSC-22 is a transcriptional regulator of the **CNP** gene and transmits signals from cytokines, such as TGF-β, for **CNP** gene expression. Both **CNP** and atrial natriuretic peptide (ANP) increased cellular cGMP levels in

anterior pituitary-derived cell lines (GH3 and AtT20/D16v-F2) in a dose-dependent manner. **CNP**, not ANP, stimulated **growth hormone** (**GH**) release from GH3 cells. On the other hand, neither ANP nOr **CNP** had any significant effect on the corticotropin release from AtT20/D16v-F2 cells. The stimulation of **GH** release from GH3 cells by **CNP** is mediated mainly by the cyclic GMP-dependent protein kinase signal transduction pathway, not by cAMP-dependent kinase nor protein kinase C pathways, through a **CNP**-specific receptor. These findings point to a novel biological function of **CNP** as an autocrine/paracrine local modulator in the anterior pituitary.

L4 ANSWER 13 OF 45 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 95317339 EMBASE
DOCUMENT NUMBER: 1995317339
TITLE: Cyclic GMP stimulates **growth hormone** release in rat anterior pituitary cells.
AUTHOR: Hartt D.J.; Ogiwara T.; Ho A.K.; Chik C.L.
CORPORATE SOURCE: Department of Physiology, University of Alberta,Edmonton, Alta. T6G 2H7, Canada
SOURCE: Biochemical and Biophysical Research Communications, (1995) Vol. 214, No. 3, pp. 918-926. .
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 951114
Last Updated on STN: 951114

AB In this study, the role of cGMP on **growth hormone** (**GH**) release was examined using a static monolayer culture prepared from dispersed rat anterior pituitary cells. Treatment with 8-bromo-cGMP (1 μM to 1 mM) stimulated **GH** release up to 3.8-fold in a concentration-dependent manner. Elevating cGMP with nitroprusside or the **C-type natriuretic peptide** was also effective in stimulating **GH** release. The increase in **GH** release by cGMP-elevating agents occurred without a concomitant increase in cAMP. Unlike cAMP which increased intracellular Ca2+ concentration, 8-bromo-cGMP caused a small reduction in intracellular Ca2+ concentration. Taken together, these results indicate that i) cGMP appears to be another mechanism that regulates **GH** release, ii) activation of cytosolic or membranous guanylyl cyclase is equally effective in stimulating **GH** release; and iii) the cGMP-induced **GH** release appears to be through a mechanism distinct from that of cAMP.

L4 ANSWER 14 OF 45 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 94194731 EMBASE
DOCUMENT NUMBER: 1994194731
TITLE: **C-type natriuretic peptide** stimulates secretion of **growth hormone** from pituitary-derived GH3 cells via a cyclic-GMP-mediated pathway.
AUTHOR: Shimekake Y.; Ohta S.; Nagata K.
CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi and Co., Ltd., 5-12-4 Sagisu,Fukushima-ku, Osaka 553, Japan
SOURCE: European Journal of Biochemistry, (1994) Vol. 222, No. 2, pp. 645-650. .
ISSN: 0014-2956 CODEN: EJBCAI
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 940803
Last Updated on STN: 940803

AB Although **C-type natriuretic peptide** (**CNP**) has been shown to exist at the highest concentration in the anterior pituitary in rat tissues, its physiological role(s) there is (are) not clear. In this study, we report a novel function of **CNP** examined with anterior pituitary-derived cell lines, GH3 and AtT20/D16v-F2. Both **CNP** and atrial natriuretic peptide (ANP) increased cellular cGMP levels in both cell lines in dose-dependent manners. **CNP**, but not ANP, stimulated **growth hormone** (**GH**) release from GH3 cells. In contrast, neither ANP nor **CNP** had any significant effect on the corticotropin release from AtT20/D16v-F2 cells. An activator for cGMP-dependent protein kinase (cGK), dibutyryl cGMP, mimicked the stimulation of **GH** release from GH3 cells by **CNP**. Constitutive **GH** release from GH3 cells was greatly diminished in the presence of inhibitors for cAMP-dependent protein kinase, while stimulative **GH** release by **CNP** was not affected. However, inhibitors which can block cGK almost completely diminished the stimulative effect of **CNP**. An inhibitor for protein kinase C did not show any effect on either constitutive or **CNP** -stimulative **GH** release. Our observations indicate that the stimulation of **GH** release from GH3 cells by **CNP** is mediated mainly by the cGK signal-transduction pathway, not by cAMP-dependent protein kinase or protein kinase C, through a **CNP** -specific receptor (possibly ANP-B receptor). Thus, **CNP** may act as a local modulator in the anterior pituitary.

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ACCESSION NUMBER: 93187650 EMBASE
DOCUMENT NUMBER: 1993187650
TITLE: Cell-type-specific function of the **C-type natriuretic peptide** gene promoter in rat anterior pituitary-derived cultured cell lines.
AUTHOR: Ohta S.; Shimekake Y.; Nagata K.
CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi and Co., Ltd., Fukushima-ku,Osaka, Osaka 553, Japan
SOURCE: Molecular and Cellular Biology, (1993) Vol. 13, No. 7, pp. 4077-4086. .
ISSN: 0270-7306 CODEN: MCEBD4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 930808
Last Updated on STN: 930808

AB The promoter function of the human **C-type natriuretic peptide** (**CNP**) gene in various cultured cells was examined by transient transfection assays. The **CNP** promoter functioned very effectively in GH3 cells, which originated from the **growth hormone**-producing tumor of the rat anterior pituitary and somatomammotroph phenotype, but functioned much less effectively in GH1 cells, another type of rat pituitary-derived cell with a somatotroph phenotype, and rat primary cardiocytes. The **CNP** promoter did not function at all in other cells, including AtT20 cells of murine pituitary corticotroph origin. Functional analyses of the deleted promoters with various 5' deletion breakpoints revealed the existence of at least two negative and one positive regulatory regions.

Within the positive regulatory region (positions -54 to - 19), which conferred 90% of the promoter activity in GH3 cells, two equipotent GC-rich cis elements (positions -49 to -45 and -40 to -35) were identified. Both sites shared half of the promoter activity and binding properties to the nuclear protein in GH3 cells. Rat anterior pituitary tissue contained the binding protein of the identified cis element, which was identical or similar to that of GH3 cells. With Southwestern (DNA-protein) analysis, a 70-kDa specific binding protein distinct from known factors such as SP-1, AP-2, and Pit-1 was identified in the nuclear extract of GH3 cells.

L4 ANSWER 16 OF 45 EMBASE 

ACCESSION NUMBER: 88242833 EMBASE
DOCUMENT NUMBER: 1988242833
TITLE: Effect of **growth hormone** on growth and myelination in the neonatal hypothyroid rat.
AUTHOR: King R.A.; Smith R.M.; Meller D.J.; Dahlenburg G.W.; Lineham J.D.
CORPORATE SOURCE: CSIRO (Australia), Division of Human Nutrition, Adelaide, SA 5000, Australia
SOURCE: Journal of Endocrinology, (1988) Vol. 119, No. 1, pp. 117-125. .
ISSN: 0022-0795 CODEN: JOENAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 003 Endocrinology
037 Drug Literature Index
030 Pharmacology
008 Neurology and Neurosurgery
021 Developmental Biology and Teratology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 911211
Last Updated on STN: 911211

AB The possible involvement of a deficit of **GH** and insulin-like growth factor-I (somatomedin C) (IGF-I/SMC) in mediating the effects of propylthiouracil (PTU)-induced hypothyroidism on body and skeletal growth and myelination was studied in the neonatal rat. Myelination (as assessed by 2',3'-cyclic nucleotide 3'-phosphohydrolase (**CNP**) activity), skeletal growth (as assessed by tail length) and body weight of pups from PTU-treated mothers were significantly retarded compared with normal animals or euthyroid controls. At 20 days after birth, plasma **GH** in hypothyroid animals was undetectable (<10 μg/l), pituitary in **GH** content was 1.2% of control, and plasma, liver and kidney IGF-I/SMC concentrations were 63, 68 and 50% of control values respectively. **CNP** activity in hypothyroid brain was 52% of normal controls but the concentration of IGF-I/SMC was 113-154% of control. Treatment of hypothyroid animals from day 1 with **GH** (10 mg/kg body weight per day) restored liver and plasma IGF-I/SMC concentrations at 20 days to values above those of normal animals and euthyroid controls. The concentration of IGF-I/SMC was also significantly ($P < 0.001$) restored in hypothyroid kidney (79% of normal), but the concentration in brain was unaffected. These observations provide evidence that the **GH** treatment employed in the present experiments was adequate to restore the deficit. **GH** treatment had no significant effect on tail length or **CNP** activity, and only a small (4-24%) effect on body weight at 20 days. Only thoroxine was able fully to restore body weight and substantially restore tail length and **CNP** activity. The present study provides strong evidence against an important involvement of **GH** or IGF-I/SMC in mediating the effects of thyroid hormone on myelination and body growth in the infant rat. It does not, however, rule out the possibility that thyroid hormone is required for the expression of the growth-promoting effects of

IGF-I/SMC by other mechanisms such as the expression of the IGF-I/SMC receptor.

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ACCESSION NUMBER: 85227946 EMBASE
DOCUMENT NUMBER: 1985227946
TITLE: Epidermal growth factor and bovine **growth hormone** stimulate differentiation and myelination of brain cell aggregates in culture.
AUTHOR: Almazan G.; Honegger P.; Matthieu J.-M.; Guentert-Lauber B.
CORPORATE SOURCE: Service de Pediatrie, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne, Switzerland
SOURCE: Developmental Brain Research, (1985) Vol. 21, No. 2, pp. 257-264. .
CODEN: DBRRDB
COUNTRY: Netherlands
DOCUMENT TYPE: Journal
FILE SEGMENT: 008 Neurology and Neurosurgery
002 Physiology
021 Developmental Biology and Teratology
003 Endocrinology
LANGUAGE: English
ENTRY DATE: Entered STN: 911210
Last Updated on STN: 911210

AB Bovine **growth hormone** (bGH) and epidermal growth factor (EGF) increased the activity of ornithine decarboxylase (ODC) in brain cell aggregates cultured in a serum-free chemically defined medium. ODC is considered as a marker of cell growth and differentiation. The effect of bGH and EGF on myelination was investigated by measuring two myelin markers, 2',3'-cyclic nucleotide 3'-phosphodiesterase (**CNP**) and myelin basic protein (MBP). EGF treatment at days 2 and 5 caused a dose-dependent increase of both myelin markers at culture day 12. This increase could still be observed at culture day 19, indicating a prolonged action of EGF. The continual presence of bGH in the culture medium produced a large accumulation of MBP at day 19. This effect was dose-dependent and required the presence of triiodothyronine (T3). In contrast, the effect of bGH on **CNP** activity did not require the presence of T3. This is the first report showing a direct effect of bGH on CNS myelination in vitro and of EGF on both MBP accumulation and ODC activity.

L4 ANSWER 18 OF 45 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:191089 BIOSIS
DOCUMENT NUMBER: PREV200300191089
TITLE: Effects of angiotensin II and natriuretic peptides of the eel on prolactin and **growth hormone** release in the tilapia, Oreochromis mossambicus.
AUTHOR(S): Eckert, Steve M.; Hirano, Tetsuya; Leedom, Thomas A.; Takei, Yoshio; Grau, E. Gordon [Reprint Author]
CORPORATE SOURCE: Department of Zoology, Hawaii Institute of Marine Biology, University of Hawaii, Coconut Island, P.O. Box 1346, Kaneohe, HI, 96744, USA
grau@hawaii.edu
SOURCE: General and Comparative Endocrinology, (February 15 2003) Vol. 130, No. 3, pp. 333-339. print.
CODEN: GCENA5. ISSN: 0016-6480.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Apr 2003
Last Updated on STN: 16 Apr 2003

AB The effects of angiotensin II (ANG II) and natriuretic peptides (NPs) of the eel (ANP, atrial natriuretic peptide; **CNP**, C-

**type natriuretic peptide**; and VNP, ventricular natriuretic peptide) on prolactin (PRL188 and PRL177) and **growth hormone** (**GH**) release from the organ-cultured tilapia pituitary were examined. Eel ANG II at concentrations greater than 1 nM stimulated the release of PRL188 and PRL177 in a dose-related manner during the first hour of incubation. Significant stimulation by 100 nM ANG II on PRL177 release was observed until 4 h of incubation, and on PRL188 release until 12 h. No effect of ANG II was seen on **GH** release. None of the NPs altered the release of PRLs at any time point. On the other hand, eel VNP at concentrations greater than 1 nM stimulated **GH** release in a dose-related manner after 4 h, and significant stimulation was observed until 48 h. Eel **CNP** was less effective than eel VNP; significant stimulation of **GH** release was observed at 1 and 10 nM during 24-48 h of incubation. No significant effect of eel ANP on **GH** release was seen at any concentration. ANG II had no effect on **GH** release at any time point. There was no change in mRNA levels of PRLs or **GH** in the pituitaries incubated with ANG II for 8 h or those incubated with the NPs for 48 h. These results indicate rapid and short-lasting stimulation by ANG II on PRL release and slow and long-lasting stimulation by VNP and **CNP** on **GH** release from the tilapia pituitary.

L4 ANSWER 19 OF 45 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:505587 BIOSIS
DOCUMENT NUMBER: PREV200200505587
TITLE: Comparison of vasodilators in human internal mammary artery: Ghrelin is a potent physiological antagonist of endothelin-1.
AUTHOR(S): Wiley, Katherine E. [Reprint author]; Davenport, Anthony P.
CORPORATE SOURCE: Clinical Pharmacology Unit, Addenbrooke's Hospital, University of Cambridge, Level 6, Centre for Clinical Investigation, Box 110, Cambridge, CB2 2QQ, UK kew29@hermes.cam.ac.uk
SOURCE: British Journal of Pharmacology, (August, 2002) Vol. 136, No. 8, pp. 1146-1152. print.
CODEN: BJPCBM. ISSN: 0007-1188.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Sep 2002
Last Updated on STN: 25 Sep 2002

AB 1 The potential vasodilator function of the peptide ghrelin, recently identified as the endogenous ligand of the **growth hormone** secretogogue orphan receptor (**GHS**-R), was investigated in human endothelium-denuded internal mammary artery. The peptide endothelin-1 (ET-1) is a potent and long-lasting vasoconstrictor. Comparisons were made with established and putative endogenous vasodilators to determine if any could reverse ET-1-induced vasoconstriction in this vessel. 2 Ghrelin (0.1-300 nM) potently dilated 10 nM ET-1-induced constrictions (pD2 8.39 +- 0.29; EMAX 63+-5.6%; n=9/14, responders/total). 3 ANP (pD2 7.75+-0.14; EMAX 106+-2.0; n = 5/5) and CGRP (pD2 8.08+-0.17; EMAX 76+-15% n = 5/6) both produced complete reversal of the constrictor response to ET-1 (EMAX not significantly different from 100%, P>0.05 one-sample t-test). 4 The following caused partial reversal of the ET-1 response: Adrenomedullin (n = 9/9) and two peptides derived from proadrenomedullin, PAMP-12 (n = 6/7) and PAMP-20 (n = 9/9) (pD2 values 7.63+-0.28, 7.97+-0.23 and 8.51+-0.29; EMAX 58+-7.3, 54+-10 and 51+-7.8% respectively). Unexpectedly, amylin was only 2 fold less potent than CGRP, although there was less than 50% reversal of the ET-1 constriction (pD2 7.86+-0.30; EMAX 41+-5.4%; n = 7/9). **CNP** (n = 6/6) also partially reversed constrictions to ET-1 (EMAX 53+-6.3; pD2 8.07+-0.38). 5 BNP (n = 4/5) and PGI2 (n = 6/8) were weak vasodilators, since concentration-response curves failed to reach a maximum within the range tested. PGE2 caused a small dilatation in some vessels (EMAX

17+-2.1%; pD2 8.63+-0.36; n = 4/8). 6 We have demonstrated ghrelin to be an effective, endothelium-independent vasodilator of the long-lasting constrictor ET-1 in human arteries producing responses similar to those of adrenomedullin (P>0.05, ANOVA).

L4 ANSWER 20 OF 45 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:347838 BIOSIS
DOCUMENT NUMBER: PREV200000347838
TITLE: **C-type natriuretic peptide (CNP)** effects in anterior pituitary cell lines: Evidence for homologous desensitisation of **CNP**-stimulated cGMP accumulation in alphaT3-1 gonadotroph-derived cells.
AUTHOR(S): Fowkes, R. C. [Reprint author]; Forrest-Owen, W.; McArdle, C. A.
CORPORATE SOURCE: Molecular Endocrinology Laboratory 1.4, St Bartholomew's and the Royal London School of Medicine and Dentistry, St Bartholomew's Close, 1st Floor Dominion House, London, EC1A 7BE, UK
SOURCE: Journal of Endocrinology, (July, 2000) Vol. 166, No. 1, pp. 195-203. print.
CODEN: JOENAK. ISSN: 0022-0795.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Aug 2000
Last Updated on STN: 7 Jan 2002

AB **C-type natriuretic peptide (CNP)**, the third member of the natriuretic peptide family, has been found at its highest tissue concentrations in the anterior pituitary, where it is localised in gonadotrophs. Its specific guanylyl cyclase-containing receptor, GC-B, is also expressed on several anterior pituitary cell types, and **CNP** potently stimulates cGMP accumulation in rat pituitary cell cultures and pituitary cell lines. The mouse gonadotroph-derived alphaT3-1 cell line has been shown to express **CNP** as well as GC-B (but not GC-A) receptors, suggesting that **CNP** may well be an autocrine regulator of gonadotrophs. Comparing effects of three natriuretic peptides (atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and **CNP**) on cGMP accumulation in four pituitary cell lines (alphaT3-1, TtT-GF, AtT-20 and GH3) we find that **CNP** is most potent and effective in alphaT3-1 cells. In these cells, **CNP**-stimulated cGMP accumulation was found to desensitise during a 30 min exposure to **CNP**. Pretreatment with **CNP** for up to 6 h also caused a significant reduction in the ability of **CNP** to subsequently stimulate cGMP accumulation. This effect was receptor specific, because pretreatment with sodium nitroprusside (an activator of nitric oxide-sensitive guanylyl cyclase), or with ANP or BNP, did not cause desensitisation of **CNP** -stimulated cGMP accumulation. Protein kinase C activation with phorbol esters also inhibited **CNP**-stimulated cGMP accumulation and such inhibition was also seen in cells desensitised by pretreatment with **CNP**. Thus it appears that the endogenous GC-B receptors of alphaT3-1 cells are subject to both homologous and heterologous desensitisation, that the mechanisms underlying these forms of desensitisation are distinct, and that cGMP elevation alone is insufficient to desensitise GC-B receptors.

L4 ANSWER 21 OF 45 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1995:509244 BIOSIS
DOCUMENT NUMBER: PREV199598514294
TITLE: Cyclic GMP stimulates **growth hormone** release in rat anterior pituitary cells.
AUTHOR(S): Hartt, Donald J.; Ogiwara, Takayui; Ho, Anthony K.; Chik,

Constance L. [Reprint author]
CORPORATE SOURCE: Room 7-33 MSB, Dep. Physiol., Univ. Alberta, Edmonton, AB T6G 2H7, Canada
SOURCE: Biochemical and Biophysical Research Communications, (1995) Vol. 214, No. 3, pp. 918-926.
CODEN: BBRCA9. ISSN: 0006-291X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Nov 1995
Last Updated on STN: 29 Nov 1995

AB In this study, the role of cGMP on **growth hormone** ( **GH**) release was examined using a static monolayer culture prepared from dispersed rat anterior pituitary cells. Treatment with 8-bromo-cGMP (1 mu-M to 1 mM) stimulated **GH** release up to 3.8-fold in a concentrationdependent manner. Elevating cGMP with nitroprusside or the **C-type natriuretic peptide** was also effective in stimulating **GH** release. The increase in **GH** release by cGMP-elevating agents occurred without a concomitant increase in cAMP. Unlike cAMP which increased intracellular Ca-2+ concentration, 8-bromo-cGMP caused a small reduction in intracellular Ca-2+ concentration. Taken together, these results indicate that i) cGMP appears to be another mechanism that regulates **GH** release, ii) activation of cytosolic or membranous guanylyl cyclase is equally effective in stimulating **GH** release; and iii) the cGMP-induced **GH** release appears to be through a mechanism distinct from that of cAMP.

```
=> dis his

     (FILE 'HOME' ENTERED AT 10:42:25 ON 14 FEB 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 10:42:38 ON 14 FEB 2006
L1          6747 S (CNP OR C(W)TYPE(W)NATRIURETIC(W)PEPTIDE)
L2            32 S L1 AND (SKELETAL(W)DYSPLASIA OR ACHONDROPLASIA OR HYPOCHONDRO
L3            16 DUP REM L2 (16 DUPLICATES REMOVED)
L4            45 S L1 AND (GH OR GROWTH(W)HORMONE)
L5            21 DUP REM L4 (24 DUPLICATES REMOVED)

=> s l5 and (fusion(w)protein or chimeric(w)protein or carrier(w)protein)
L6             2 L5 AND (FUSION(W) PROTEIN OR CHIMERIC(W) PROTEIN OR CARRIER(W)
                 PROTEIN)

=> dup rem
ENTER L# LIST OR (END):l6
PROCESSING COMPLETED FOR L6
L7             2 DUP REM L6 (0 DUPLICATES REMOVED)

=> dis ibib abs l7 1-2

L7   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2005:902731  CAPLUS
DOCUMENT NUMBER:          143:253860
TITLE:                    Albumin fusion proteins for
                          prolonged shelf-life of therapeutic proteins
INVENTOR(S):              Rosen, Craig A.; Haseltine, William A.; Moore, Paul
                          A.; Bock, Jason B.; Bell, Adam; Shi, Yanggu; Lafleur,
                          David
PATENT ASSIGNEE(S):       Human Genome Sciences, Inc., USA
SOURCE:                   PCT Int. Appl., 603 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
```

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005077042 | A2 | 20050825 | WO 2005-US4041 | 20050209 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| PRIORITY APPLN. INFO.: | | |
|---|---|---|
| US 2004-542274P | P | 20040209 |
| US 2004-549901P | P | 20040305 |
| US 2004-556906P | P | 20040329 |
| US 2004-636603P | P | 20041217 |

AB The present invention encompasses albumin **fusion proteins**. Many therapeutic proteins in their native state or when recombinantly produced are typically labile mols. exhibiting short shelf-lives, particularly when formulated in aqueous solns.; fusions of the therapeutic protein with human serum albumin have a longer serum half-life and/or stabilized activity in solution (or in a pharmaceutical composition) in vitro and/or in vivo than the corresponding unfused therapeutic mols. Thus, albumin **fusion proteins** are provided comprising granulocyte colony-stimulating factor, interleukin 2, parathormone, erythropoietin, interferon β, interferon α2, interferon A/D hybrid, a single-chain insulin analog, **growth hormone**, and (7-36)GLP-1. Nucleic acid mols. encoding the albumin **fusion proteins** of the invention are also encompassed by the invention, as are vectors containing these nucleic acids, host cells transformed with these nucleic acids vectors, and methods of making the albumin **fusion proteins** of the invention and using these nucleic acids, vectors, and/or host cells. Addnl., the present invention encompasses pharmaceutical compns. comprising albumin **fusion proteins** and methods of treating or preventing diseases, disorders or conditions related to diabetes mellitus using albumin **fusion proteins** of the invention.

L7 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN

| | |
|---|---|
| ACCESSION NUMBER: | 2005:902703 CAPLUS |
| DOCUMENT NUMBER: | 143:272498 |
| TITLE: | Gene expression profiles in the diagnosis and treatment of Alzheimer's disease |
| INVENTOR(S): | Landfield, Philip W.; Porter, Nada M.; Chen, Kuey Chu; Geddes, James; Blalock, Eric |
| PATENT ASSIGNEE(S): | University of Kentucky Research Foundation, USA |
| SOURCE: | PCT Int. Appl., 114 pp.<br>CODEN: PIXXD2 |
| DOCUMENT TYPE: | Patent |
| LANGUAGE: | English |
| FAMILY ACC. NUM. COUNT: | 1 |

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005076939 | A2 | 20050825 | WO 2005-US3668 | 20050209 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,

NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-542281P P 20040209

AB Genes showing altered patterns of expression in the brain that are associated with the neurol. changes found in Alzheimer's disease and that can be used in the early diagnosis of the disease, including the incipient form of the disease, are identified. The methods and kits of the invention utilize a set of genes and their encoded proteins that are shown to be correlated with incipient Alzheimer's disease.

```
     (FILE 'HOME' ENTERED AT 10:42:25 ON 14 FEB 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 10:42:38 ON 14 FEB 2006
L1          6747 S (CNP OR C(W)TYPE(W)NATRIURETIC(W)PEPTIDE)
L2            32 S L1 AND (SKELETAL(W)DYSPLASIA OR ACHONDROPLASIA OR HYPOCHONDRO
L3            16 DUP REM L2 (16 DUPLICATES REMOVED)
L4            45 S L1 AND (GH OR GROWTH(W)HORMONE)
L5            21 DUP REM L4 (24 DUPLICATES REMOVED)
L6             2 S L5 AND (FUSION(W)PROTEIN OR CHIMERIC(W)PROTEIN OR CARRIER(W)
L7             2 DUP REM L6 (0 DUPLICATES REMOVED)

=> dis ibib abs l5 1-21

L5   ANSWER 1 OF 21  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2005:1103612  CAPLUS
DOCUMENT NUMBER:          143:385164
TITLE:                    Antibody specific to mammalian endogenous ligand
                          without neutralizing activity for stabilizing ligand
                          and enhancing receptor activity to treat diseases
INVENTOR(S):              Inooka, Hiroshi; Suzuki, Nobuhiro; Kokubo, Toshio;
                          Kurokawa, Tomofumi
PATENT ASSIGNEE(S):       Takeda Pharmaceutical Company Limited, Japan
SOURCE:                   PCT Int. Appl., 98 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.            KIND   DATE        APPLICATION NO.         DATE
     ----------------      ----   --------    --------------------    --------
     WO 2005094881          A1    20051013    WO 2005-JP6576          20050329
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM,
             SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                       JP 2004-98595       A  20040330
AB   An ameliorating agent for the stability of mammalian endogenous ligand in
     the blood, comprising an antibody having affinity with mammalian
     endogenous ligand and substantially not neutralizing the same; and prepns.
     thereof for the prevention and treatment of diseases in accomplishment of
     which it is effective to increase the concentration of endogenous ligand in the
     blood and/or prolong the half life period thereof in the blood.  When the
     prepns. alone without being combined with a compound identical with or
     substantially identical with the endogenous ligand are administered to a
     mammal, the stability of endogenous ligand in the blood would be enhanced
     to thereby reinforce the receptor activity regulating action thereof.  The
     endogenous ligand belonging to the secretin/glucagon superfamily is
     selected from GLP-1, calcitonin, PACAP, VIP, LHRH, metastin, GPR7/GPR8
     ligand, MSH, ghrelin, apelin, EPO, TPO, insulin, interferon,
     growth hormone, GM-CSF, leptin, adiponectin, ANP, BNP,
     CNP, betacellulin, betacellulin-γ4, adrenomedullin.
REFERENCE COUNT:          11    THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5   ANSWER 2 OF 21  CAPLUS  COPYRIGHT 2006 ACS on STN
```

ACCESSION NUMBER: 2005:902731 CAPLUS
DOCUMENT NUMBER: 143:253860
TITLE: Albumin fusion proteins for prolonged shelf-life of therapeutic proteins
INVENTOR(S): Rosen, Craig A.; Haseltine, William A.; Moore, Paul A.; Bock, Jason B.; Bell, Adam; Shi, Yanggu; Lafleur, David
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA
SOURCE: PCT Int. Appl., 603 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005077042 | A2 | 20050825 | WO 2005-US4041 | 20050209 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 2004-542274P | P | 20040209 |
| US 2004-549901P | P | 20040305 |
| US 2004-556906P | P | 20040329 |
| US 2004-636603P | P | 20041217 |

AB The present invention encompasses albumin fusion proteins. Many therapeutic proteins in their native state or when recombinantly produced are typically labile mols. exhibiting short shelf-lives, particularly when formulated in aqueous solns.; fusions of the therapeutic protein with human serum albumin have a longer serum half-life and/or stabilized activity in solution (or in a pharmaceutical composition) in vitro and/or in vivo than the corresponding unfused therapeutic mols. Thus, albumin fusion proteins are provided comprising granulocyte colony-stimulating factor, interleukin 2, parathormone, erythropoietin, interferon β, interferon α2, interferon A/D hybrid, a single-chain insulin analog, **growth hormone**, and (7-36)GLP-1. Nucleic acid mols. encoding the albumin fusion proteins of the invention are also encompassed by the invention, as are vectors containing these nucleic acids, host cells transformed with these nucleic acids vectors, and methods of making the albumin fusion proteins of the invention and using these nucleic acids, vectors, and/or host cells. Addnl., the present invention encompasses pharmaceutical compns. comprising albumin fusion proteins and methods of treating or preventing diseases, disorders or conditions related to diabetes mellitus using albumin fusion proteins of the invention.

L5 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:902703 CAPLUS
DOCUMENT NUMBER: 143:272498
TITLE: Gene expression profiles in the diagnosis and treatment of Alzheimer's disease
INVENTOR(S): Landfield, Philip W.; Porter, Nada M.; Chen, Kuey Chu; Geddes, James; Blalock, Eric
PATENT ASSIGNEE(S): University of Kentucky Research Foundation, USA
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2005076939 | A2 | 20050825 | WO 2005-US3668 | 20050209 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-542281P P 20040209

AB Genes showing altered patterns of expression in the brain that are associated with the neurol. changes found in Alzheimer's disease and that can be used in the early diagnosis of the disease, including the incipient form of the disease, are identified. The methods and kits of the invention utilize a set of genes and their encoded proteins that are shown to be correlated with incipient Alzheimer's disease.

L5 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1036916 CAPLUS
DOCUMENT NUMBER: 142:33307
TITLE: Stable analogs of peptide and polypeptide therapeutics
INVENTOR(S): Bachovchin, William W.; Lai, Hung-Sen; Sanford, David George
PATENT ASSIGNEE(S): Trustees of Tufts College, USA
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004103390 | A2 | 20041202 | WO 2004-US15488 | 20040517 |
| WO 2004103390 | A3 | 20050630 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| US 2005049177 | A1 | 20050303 | US 2004-847220 | 20040517 |

PRIORITY APPLN. INFO.: US 2003-471411P P 20030515

AB The present invention relates to compns. of peptide and polypeptide analogs that are resistant to proteolysis, pharmaceutical uses thereof, and methods of preparation thereof. The peptide and polypeptide analogs are resistant to cleavage by proteinases, i.e., a serine proteinase, metalloproteinase, aspartic proteinase, or cysteine e proteinase. For example, two substitutions at the P'1 glutamic acid of GLP1-(7-37) were made to obtain GLP-1 (3DMA), wherein the P'1 substitution was

3-dimethylaspartate, and GLP-1-(BM), wherein the P'1 substitution was 3-butylmethylglycine. Both GLP-1 (3DMA) and GLP-1-(BM) displayed robust resistance to degradation by the serine protease dipeptidyl peptidase IV (DPP IV) and retained biol. activities of native glucagon-like peptide 1 (GLP-1). They both retained the ability to bind to GLP-1 receptors of COS-7 cells, as well as to potentiate GLP-1 signaling via the GLP-1 receptor to an extent indistinguishable from native GLP-1.

L5 ANSWER 5 OF 21 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003094867 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12606276
TITLE: Effects of angiotensin II and natriuretic peptides of the eel on prolactin and **growth hormone** release in the tilapia, Oreochromis mossambicus.
AUTHOR: Eckert Steve M; Hirano Tetsuya; Leedom Thomas A; Takei Yoshio; Gordon Grau E
CORPORATE SOURCE: Department of Zoology and Hawaii Institute of Marine Biology, University of Hawaii, PO Box 1346, Coconut Island, Kaneohe, HI 96744, USA.
SOURCE: General and comparative endocrinology, (2003 Feb 15) 130 (3) 333-9.
Journal code: 0370735. ISSN: 0016-6480.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030228
Last Updated on STN: 20031024
Entered Medline: 20031023

AB The effects of angiotensin II (ANG II) and natriuretic peptides (NPs) of the eel (ANP, atrial natriuretic peptide; **CNP**, **C-type natriuretic peptide**; and VNP, ventricular natriuretic peptide) on prolactin (PRL(188) and PRL(177)) and **growth hormone** (**GH**) release from the organ-cultured tilapia pituitary were examined. Eel ANG II at concentrations greater than 1 nM stimulated the release of PRL(188) and PRL(177) in a dose-related manner during the first hour of incubation. Significant stimulation by 100 nM ANG II on PRL(177) release was observed until 4h of incubation, and on PRL(188) release until 12 h. No effect of ANG II was seen on **GH** release. None of the NPs altered the release of PRLs at any time point. On the other hand, eel VNP at concentrations greater than 1 nM stimulated **GH** release in a dose-related manner after 4 h, and significant stimulation was observed until 48 h. Eel **CNP** was less effective than eel VNP; significant stimulation of **GH** release was observed at 1 and 10 nM during 24-48 h of incubation. No significant effect of eel ANP on **GH** release was seen at any concentration. ANG II had no effect on **GH** release at any time point. There was no change in mRNA levels of PRLs or **GH** in the pituitaries incubated with ANG II for 8 h or those incubated with the NPs for 48 h. These results indicate rapid and short-lasting stimulation by ANG II on PRL release and slow and long-lasting stimulation by VNP and **CNP** on **GH** release from the tilapia pituitary.


L5 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:946130 CAPLUS
DOCUMENT NUMBER: 138:29120
TITLE: Preparation of peptide drug-alkylene glycol oligomer conjugates
INVENTOR(S): Ekwuribe, Nnochiri N.; Price, Christopher H.; Ansari, Aslam M.; Odenbaugh, Amy L.
PATENT ASSIGNEE(S): Nobex Corporation, USA

SOURCE: PCT Int. Appl., 201 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002098446 | A1 | 20021212 | WO 2002-US17567 | 20020604 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2003228275 | A1 | 20031211 | US 2001-873797 | 20010604 |
| US 6858580 | B2 | 20050222 | | |
| BR 2001006401 | A | 20030211 | BR 2001-6401 | 20011011 |
| JP 2003104913 | A2 | 20030409 | JP 2001-317307 | 20011015 |
| EP 1404355 | A1 | 20040407 | EP 2002-737357 | 20020604 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| US 2005136032 | A1 | 20050623 | US 2005-31108 | 20050107 |
| PRIORITY APPLN. INFO.: | | | US 2001-873797 A | 20010604 |
| | | | WO 2002-US17567 W | 20020604 |

OTHER SOURCE(S): MARPAT 138:29120

AB A non-polydispersed mixture of conjugates in which each conjugate in the mixture comprises a peptide drug coupled to an oligomer that includes a polyalkylene glycol moiety is disclosed. The mixture may exhibit higher in vivo activity than a polydispersed mixture of similar conjugates. The mixture may be more effective at surviving an in vitro model of intestinal digestion than polydispersed mixts. of similar conjugates. The mixture may result in less inter-subject variability than polydispersed mixts. of similar conjugates. Thus, non-polydispersed hexaethylene glycol was treated with phosgene solution, followed by treatment with N-hydroxysuccinimide (NHS) to give give the NHS ester. Human **growth hormone** (Saizen) was allowed to react with the NHS ester to give the conjugate.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 21 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002408895 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12163347
TITLE: Comparison of vasodilators in human internal mammary artery: ghrelin is a potent physiological antagonist of endothelin-1.
AUTHOR: Wiley Katherine E; Davenport Anthony P
CORPORATE SOURCE: Clinical Pharmacology Unit, University of Cambridge, Level 6, Centre for Clinical Investigation, Box 110, Addenbrooke's Hospital, UK.. kew29@hermes.cam.ac.uk
SOURCE: British journal of pharmacology, (2002 Aug) 136 (8) 1146-52.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304

ENTRY DATE: Entered STN: 20020807
Last Updated on STN: 20030429
Entered Medline: 20030428

AB 1 The potential vasodilator function of the peptide ghrelin, recently identified as the endogenous ligand of the **growth hormone** secretagogue orphan receptor (**GHS**-R), was investigated in human endothelium-denuded internal mammary artery. The peptide endothelin-1 (ET-1) is a potent and long-lasting vasoconstrictor. Comparisons were made with established and putative endogenous vasodilators to determine if any could reverse ET-1-induced vasoconstriction in this vessel. 2 Ghrelin (0.1-300 nM) potently dilated 10 nM ET-1-induced constrictions (pD(2) 8.39+/-0.29; E(MAX) 63+/-5.6%; n=9/14, responders/total). 3 ANP (pD(2) 7.75+/-0.14; E(MAX) 106+/-2.0; n=5/5) and CGRP (pD(2) 8.08+/-0.17; E(MAX) 76+/-15% n=5/6) both produced complete reversal of the constrictor response to ET-1 (E(MAX) not significantly different from 100%, P>0.05 one-sample t-test). 4 The following caused partial reversal of the ET-1 response: Adrenomedullin (n=9/9) and two peptides derived from proadrenomedullin, PAMP-12 (n=6/7) and PAMP-20 (n=9/9) (pD(2) values 7.63+/-0.28, 7.97+/-0.23 and 8.51+/-0.29; E(MAX) 58+/-7.3, 54+/-10 and 51+/-7.8% respectively). Unexpectedly, amylin was only 2 fold less potent than CGRP, although there was less than 50% reversal of the ET-1 constriction (pD(2) 7.86+/-0.30; E(MAX) 41+/-5.4%; n=7/9). **CNP** (n=6/6) also partially reversed constrictions to ET-1 (E(MAX) 53+/-6.3; pD(2) 8.07+/-0.38). 5 BNP (n=4/5) and PGI(2) (n=6/8) were weak vasodilators, since concentration-response curves failed to reach a maximum within the range tested. PGE(2) caused a small dilatation in some vessels (E(MAX) 17+/-2.1%; pD(2) 8.63+/-0.36; n=4/8). 6 We have demonstrated ghrelin to be an effective, endothelium-independent vasodilator of the long-lasting constrictor ET-1 in human arteries producing responses similar to those of adrenomedullin (P>0.05, ANOVA). British Journal of Pharmacology (2002) 136, 1146-1152

L5 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:676999 CAPLUS
DOCUMENT NUMBER: 135:252790
TITLE: Single nucleotide polymorphisms in human genes
INVENTOR(S): Cargill, Michele; Ireland, James S.; Lander, Eric S.
PATENT ASSIGNEE(S): Whitehead Institute for Biomedical Research, USA
SOURCE: PCT Int. Appl., 145 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2001066800 | A2 | 20010913 | WO 2001-US7268 | | 20010307 |
| WO 2001066800 | A3 | 20030605 | | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | | |
| US 2002032319 | A1 | 20020314 | US 2001-801274 | | 20010307 |
| PRIORITY APPLN. INFO.: | | | US 2000-187510P | P | 20000307 |
| | | | US 2000-206129P | P | 20000522 |

AB The invention provides nucleic acid segments of the human genome, particularly nucleic acid segments from genes including polymorphic sites.

The polymorphisms were identified by resequencing of target sequences from individuals of diverse ethnic and geog. backgrounds by hybridization to probes immobilized to microfabricated arrays. Some of the single nucleotide polymorphisms (SNPs) specify a different amino acid sequence, some are silent or are in noncoding regions, and some specify a stop signal in protein translation. Allele-specific primers and probes hybridizing to regions flanking or containing these sites are also provided. The nucleic acids, primers and probes are used in applications such as phenotype correlations, forensics, paternity testing, medicine and genetic anal.

L5 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:824291 CAPLUS
DOCUMENT NUMBER: 134:21425
TITLE: Protection of endogenous therapeutic peptides from peptidase activity through conjugation to blood components
INVENTOR(S): Bridon, Dominique P.; Ezrin, Alan M.; Milner, Peter G.; Holmes, Darren L.; Thibaudeau, Karen
PATENT ASSIGNEE(S): Conjuchem, Inc., Can.
SOURCE: PCT Int. Appl., 733 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000069900 | A2 | 20001123 | WO 2000-US13576 | 20000517 |
| WO 2000069900 | A3 | 20010215 | | |
| WO 2000069900 | C2 | 20020704 | | |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2373252 | AA | 20001123 | CA 2000-2373252 | 20000517 |
| CA 2373680 | AA | 20001123 | CA 2000-2373680 | 20000517 |
| CA 2499211 | AA | 20001123 | CA 2000-2499211 | 20000517 |
| CA 2501421 | AA | 20001123 | CA 2000-2501421 | 20000517 |
| CA 2505617 | AA | 20001123 | CA 2000-2505617 | 20000517 |
| WO 2000070665 | A2 | 20001123 | WO 2000-IB763 | 20000517 |
| WO 2000070665 | A3 | 20010419 | | |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1105409 | A2 | 20010613 | EP 2000-936023 | 20000517 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| EP 1171582 | A2 | 20020116 | EP 2000-929748 | 20000517 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| EP 1264840 | A1 | 20021211 | EP 2002-14617 | 20000517 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, | | | | |

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|---|---|---|---|---|---|
| | IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| JP 2003500341 | | T2 | 20030107 | JP 2000-619018 | 20000517 |
| JP 2003508350 | | T2 | 20030304 | JP 2000-618316 | 20000517 |
| AU 765753 | | B2 | 20030925 | AU 2000-51393 | 20000517 |
| EP 1591453 | | A1 | 20051102 | EP 2005-105384 | 20000517 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| EP 1598365 | | A1 | 20051123 | EP 2005-105387 | 20000517 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| EP 1623994 | | A2 | 20060208 | EP 2005-108328 | 20000517 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| US 6849714 | | B1 | 20050201 | US 2000-623548 | 20000905 |
| US 6514500 | | B1 | 20030204 | US 2000-657332 | 20000907 |
| ZA 2001006676 | | A | 20020719 | ZA 2001-6676 | 20010814 |
| ZA 2001009110 | | A | 20020613 | ZA 2001-9110 | 20011105 |
| US 2003108567 | | A1 | 20030612 | US 2002-287892 | 20021104 |
| US 6821949 | | B2 | 20041123 | | |
| US 2003108568 | | A1 | 20030612 | US 2002-288340 | 20021104 |
| US 6887849 | | B2 | 20050503 | | |
| US 2004127398 | | A1 | 20040701 | US 2003-722733 | 20031125 |
| US 2004138100 | | A1 | 20040715 | US 2003-723099 | 20031125 |
| US 2005176641 | | A1 | 20050811 | US 2005-40810 | 20050121 |
| US 2005176643 | | A1 | 20050811 | US 2005-67556 | 20050225 |
| JP 2005263807 | | A2 | 20050929 | JP 2005-115175 | 20050412 |
| JP 2005239736 | | A2 | 20050908 | JP 2005-140407 | 20050512 |
| JP 2005255689 | | A2 | 20050922 | JP 2005-151458 | 20050524 |
| US 2006009377 | | A1 | 20060112 | US 2005-170967 | 20050629 |
| PRIORITY APPLN. INFO.: | | | | US 1999-134406P | P 19990517 |
| | | | | US 1999-153406P | P 19990910 |
| | | | | US 1999-159783P | P 19991015 |
| | | | | CA 2000-2363712 | A3 20000517 |
| | | | | CA 2000-2373680 | A3 20000517 |
| | | | | EP 2000-932570 | A3 20000517 |
| | | | | EP 2000-936023 | A3 20000517 |
| | | | | JP 2000-618316 | A3 20000517 |
| | | | | JP 2000-618327 | A3 20000517 |
| | | | | WO 2000-IB763 | W 20000517 |
| | | | | WO 2000-US13576 | W 20000517 |
| | | | | US 2000-623548 | A1 20000905 |
| | | | | US 2000-657276 | A2 20000907 |
| | | | | US 2000-657332 | A3 20000907 |
| | | | | US 2002-400199P | P 20020731 |
| | | | | US 2002-400413P | P 20020731 |
| | | | | US 2002-288340 | A1 20021104 |
| | | | | WO 2003-CA1097 | W 20030729 |
| | | | | US 2003-471348 | B1 20030908 |
| | | | | US 2003-722733 | A1 20031125 |
| | | | | US 2005-40810 | A2 20050121 |

AB A method for protecting a peptide from peptidase activity in vivo, the peptide being composed of between 2 and 50 amino acids and having a C-terminus and an N-terminus and a C-terminus amino acid and an N-terminus amino acid is described. In the first step of the method, the peptide is modified by attaching a reactive group to the C-terminus amino acid, to the N-terminus amino acid, or to an amino acid located between the N-terminus and the C-terminus, such that the modified peptide is capable of forming a covalent bond in vivo with a reactive functionality on a blood component. The solid phase peptide synthesis of a number of derivs. with 3-maleimidopropionic acid (3-MPA) is described. In the next step, a covalent bond is formed between the reactive group and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase activity. The final step of the method involves the analyzing of the stability of the

peptide-blood component conjugate to assess the protection of the peptide from peptidase activity. Thus, the percentage of a K5 kringle peptide (Pro-Arg-Lys-Leu-Tyr-Asp-Lys-NH2) conjugated to human serum albumin via MPA remained relatively constant through a 24-h plasma assay in contrast to unmodified K5 which decreased to 9% of the original amount of K5 in only 4 h in plasma.

L5 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:463463 CAPLUS
DOCUMENT NUMBER: 135:37161
TITLE: Efficient genetic engineering process for preparing polypeptide medicines
INVENTOR(S): Sun, Ziyong; Liu, Jianning
PATENT ASSIGNEE(S): Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 63 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 1273248 | A | 20001115 | CN 1999-120613 | 19991213 |
| CN 1121411 | B | 20030917 | | |
| PRIORITY APPLN. INFO.: | | | CN 1999-120613 A | 19991213 |
| | | | CN 1999-114570 | 19991124 |

AB The process comprises synthesizing polypeptide with enzymolysis sites and linkers, amplifying by PCR, digesting with enzymes, transferring TOPO-type carrier, amplifying to obtain dimer, repeating the digesting, transferring, and amplifying several time to obtain multi-polypeptide; transferring into E. coli BL21(DE3), expressing, collecting mycelium, purifying on affinity chromatog. column; decomposing, and reprocessing. The linkers and decomposition methods for various types of polypeptides are presented. The process is used for preparation of polypeptide fragment such as leptin, fibronectin, Lys-Thymic factor, mast cell degranulating peptide, thymosin alpha1, GRF, angiogenin, neuropeptide Y, vasonatrin, Tyr-CRF, thymopoietin II, thymosin beta10, tritrypticin, RGD peptide II, cecropin A, CD36, bradykinin potentiator C, bradykinin potentiator B, thymus and activation regulated chemokine, defensin HNP-I, HIV gp120, basic FGF, parasin I, TNF alpha, WP9QY, urinary trypsin inhibitor, alpha-conotoxin GI, alpha-conotoxin MI, intercellular adhesion mol., tachyplesin I, polyphemusin II-derived peptide, endotoxin inhibitor, magainin I, magainin II, fibronectin adhesion promoting peptide, ACTH, cecropin B, **c-type natriuretic peptide**, LHRH, c-reactive protein, glycoprotein IIb, laminin, hirullin, and erythropoietin mimetic peptide, etc.

L5 ANSWER 11 OF 21 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2000397230 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10856898
TITLE: **C-type natriuretic peptide (CNP)** effects in anterior pituitary cell lines: evidence for homologous desensitisation of **CNP**-stimulated cGMP accumulation in alpha T3-1 gonadotroph-derived cells.
AUTHOR: Fowkes R C; Forrest-Owen W; McArdle C A
CORPORATE SOURCE: Division of Medicine, Department of Hospital Medicine, University of Bristol, Bristol Royal Infirmary, Marlborough Street, Bristol BS2 8HW, UK.. r.c.fowlkes@mds.qmw.ac.uk
SOURCE: Journal of endocrinology, (2000 Jul) 166 (1) 195-203.
Journal code: 0375363. ISSN: 0022-0795.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000824
Last Updated on STN: 20000824
Entered Medline: 20000817

AB **C-type natriuretic peptide** (**CNP**), the third member of the natriuretic peptide family, has been found at its highest tissue concentrations in the anterior pituitary, where it is localised in gonadotrophs. Its specific guanylyl cyclase-containing receptor, GC-B, is also expressed on several anterior pituitary cell types, and **CNP** potently stimulates cGMP accumulation in rat pituitary cell cultures and pituitary cell lines. The mouse gonadotroph-derived alpha T3-1 cell line has been shown to express **CNP** as well as GC-B (but not GC-A) receptors, suggesting that **CNP** may well be an autocrine regulator of gonadotrophs. Comparing effects of three natriuretic peptides (atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and **CNP**) on cGMP accumulation in four pituitary cell lines (alpha T3-1, TtT-GF, AtT-20 and **GH** (3)) we find that **CNP** is most potent and effective in alpha T3-1 cells. In these cells, **CNP**-stimulated cGMP accumulation was found to desensitise during a 30 min exposure to **CNP**. Pretreatment with **CNP** for up to 6 h also caused a significant reduction in the ability of **CNP** to subsequently stimulate cGMP accumulation. This effect was receptor specific, because pretreatment with sodium nitroprusside (an activator of nitric oxide-sensitive guanylyl cyclase), or with ANP or BNP, did not cause desensitisation of **CNP** -stimulated cGMP accumulation. Protein kinase C activation with phorbol esters also inhibited **CNP**-stimulated cGMP accumulation and such inhibition was also seen in cells desensitised by pretreatment with **CNP**. Thus it appears that the endogenous GC-B receptors of alpha T3-1 cells are subject to both homologous and heterologous desensitisation, that the mechanisms underlying these forms of desensitisation are distinct, and that cGMP elevation alone is insufficient to desensitise GC-B receptors.

L5 ANSWER 12 OF 21 EMBASE  DUPLICATE 4
ACCESSION NUMBER: 97029822 EMBASE
DOCUMENT NUMBER: 1997029822
TITLE: **C-type natriuretic peptide**: Regulatory mechanism of gene expression and novel biological function.
AUTHOR: Nagata K.; Shimekake Y.; Ohta S.
CORPORATE SOURCE: Y. Shimekake, DNAVEC Research Inc., 25-11 Kannondai 1-Chome, Tsukuba-shi, Ibaragi 305, Japan
SOURCE: Annual Report of Shionogi Research Laboratory, (1996) No. 46, pp. 24-47. .
Refs: 80
ISSN: 0559-8680 CODEN: SKNEA7
COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 970218
Last Updated on STN: 970218

AB The promoter of human **C-type natriuretic peptide** (**CNP**) gene functions very effectively in rat anterior pituitary-derived GH3 cells. Extensive functional analysis of **CNP** promoter revealed the existence of a positive regulatory region consisting of two GC-rich sequence elements which fire equipotent in DNA binding specificity and transcriptional activity and confer 90% of

the promoter function. The promoter function of the positive regulatory region was stimulated by transforming growth factor (TGF) -β or other cytokines. The transcription factor affecting the GC-rich element was cloned by Southwestern screening, and identified as TSC-22 which was originally isolated from mouse osteoblastoma cells as a TGF-β stimulated clone. TSC-22 stimulated the **CNP** promoter function when it was transiently expressed in GH3 as well as in human aortic endothelial cells (HAEC). TSC-22 gene expression in GH3 and HAEC was stimulated by cytokines including TGF- β, in correlation with the **CNP** mRNA increase, suggesting that TSC-22 is a transcriptional regulator of the **CNP** gene and transmits signals from cytokines, such as TGF-β, for **CNP** gene expression. Both **CNP** and atrial natriuretic peptide (ANP) increased cellular cGMP levels in anterior pituitary-derived cell lines (GH3 and AtT20/D16v-F2) in a dose-dependent manner. **CNP**, not ANP, stimulated **growth hormone** (**GH**) release from GH3 cells. On the other hand, neither ANP nOr **CNP** had any significant effect on the corticotropin release from AtT20/D16v-F2 cells. The stimulation of **GH** release from GH3 cells by **CNP** is mediated mainly by the cyclic GMP-dependent protein kinase signal transduction pathway, not by cAMP-dependent kinase nor protein kinase C pathways, through a **CNP**-specific receptor. These findings point to a novel biological function of **CNP** as an autocrine/paracrine local modulator in the anterior pituitary.

L5 ANSWER 13 OF 21 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 96024586 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7575564
TITLE: Cyclic GMP stimulates **growth hormone** release in rat anterior pituitary cells.
AUTHOR: Hartt D J; Ogiwara T; Ho A K; Chik C L
CORPORATE SOURCE: Department of Medicine, Faculty of Medicine, University of Alberta, Edmonton, Canada.
SOURCE: Biochemical and biophysical research communications, (1995 Sep 25) 214 (3) 918-26.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19990129
Entered Medline: 19951102

AB In this study, the role of cGMP on **growth hormone** (**GH**) release was examined using a static monolayer culture prepared from dispersed rat anterior pituitary cells. Treatment with 8-bromo-cGMP (1 microM to 1 mM) stimulated **GH** release up to 3.8-fold in a concentration-dependent manner. Elevating cGMP with nitroprusside or the **C-type natriuretic peptide** was also effective in stimulating **GH** release. The increase in **GH** release by cGMP-elevating agents occurred without a concomitant increase in cAMP. Unlike cAMP which increased intracellular Ca2+ concentration, 8-bromo-cGMP caused a small reduction in intracellular Ca2+ concentration. Taken together, these results indicate that i) cGMP appears to be another mechanism that regulates **GH** release, ii) activation of cytosolic or membranous guanylyl cyclase is equally effective in stimulating **GH** release; and iii) the cGMP-induced **GH** release appears to be through a mechanism distinct from that of cAMP.

L5 ANSWER 14 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1995:62049 BIOSIS
DOCUMENT NUMBER: PREV199598076349

TITLE: **C-type natriuretic peptide (CNP)** in the pituitary: Is **CNP** an autocrine regulator of gonadotropes?.

AUTHOR(S): McArdle, Craig A. [Reprint author]; Olcese, James; Schmidt, Carola; Poch, Annette; Kratzmeier, Martin; Middendorff, Ralf

CORPORATE SOURCE: Dep. Med., University Bristol, Marlborough St., Bristol BS2 8HW, UK

SOURCE: Endocrinology, (1994) Vol. 135, No. 6, pp. 2794-2801.
CODEN: ENDOAO. ISSN: 0013-7227.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 8 Feb 1995
Last Updated on STN: 9 Feb 1995

AB Natriuretic peptides act via receptors with intrinsic guanylate cyclase activity to stimulate cGMP production and are thought to be important regulators of neuroendocrine systems. **C-Type natriuretic peptide (CNP)** is of particular interest in this regard because the highest tissue concentrations of **CNP** occur in the anterior pituitary, where it is a highly potent stimulator of cGMP production. Here we show that pituitaries of rats and mice contain abundant **CNP** prohormone messenger RNA (mRNA), but no atrial natriuretic peptide or B-type natriuretic peptide prohormone mRNAs. Using reverse transcriptase-polymerase chain reaction, both A- and B-type natriuretic peptide receptor (GC-A and GC-B, respectively) transcripts were detected in rat and mouse pituitaries, although only the GC-B mRNA was measurable by Northern blotting. Immunohistochemistry revealed **CNP**-positive cells in the anterior, but not posterior, pituitaries of rats, and the vast majority of these cells were identified as gonadotropes by colocalization of **CNP** and LH immunoreactivities. Targeted toxicity using GnRH conjugated to the ricin-A chain was used to test whether gonadotropes are also direct targets for GnRH action. The conjugate dose dependently inhibited the proliferation of alpha-T3-1 cells (gonadotrope-derived cells with GnRH receptors), but had no such effect on **GH**-3 cells (which do not have GnRH receptors). Culture of rat pituitary cells with the conjugate caused comparable reductions in **CNP**-stimulated cGMP production, GnRH-stimulated LH release, and Ca-2+ ionophore (A23187)-stimulated LH release, but did not measurably alter cAMP production in response to pituitary adenylate cyclase-activating polypeptide. We conclude that **CNP** is synthesized in the pituitary, where it is located predominantly in gonadotropes, and GC-B receptors expressed in the pituitary mediate the direct effects of **CNP** in gonadotropes. Together with the recent demonstration of **CNP** synthesis and action in alpha-T3-1 cells, the data suggest **CNP** to be a novel autocrine regulator of gonadotropes.

L5 ANSWER 15 OF 21 MEDLINE on STN DUPLICATE 6

ACCESSION NUMBER: 94291663 MEDLINE

DOCUMENT NUMBER: PubMed ID: 8020502

TITLE: **C-type natriuretic peptide** stimulates secretion of **growth hormone** from rat-pituitary-derived GH3 cells via a cyclic-GMP-mediated pathway.

AUTHOR: Shimekake Y; Ohta S; Nagata K

CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi & Co. Ltd., Osaka, Japan.

SOURCE: European journal of biochemistry / FEBS, (1994 Jun 1) 222 (2) 645-50.
Journal code: 0107600. ISSN: 0014-2956.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940815
Last Updated on STN: 19990129
Entered Medline: 19940804

AB Although **C-type natriuretic peptide** (**CNP**) has been shown to exist at the highest concentration in the anterior pituitary in rat tissues, its physiological role(s) there is (are) not clear. In this study, we report a novel function of **CNP** examined with anterior pituitary-derived cell lines, GH3 and AtT20/D16v-F2. Both **CNP** and atrial natriuretic peptide (ANP) increased cellular cGMP levels in both cell lines in dose-dependent manners. **CNP**, but not ANP, stimulated **growth hormone** (**GH**) release from GH3 cells. In contrast, neither ANP nor **CNP** had any significant effect on the corticotropin release from AtT20/D16v-F2 cells. An activator for cGMP-dependent protein kinase (cGK), dibutyryl cGMP, mimicked the stimulation of **GH** release from GH3 cells by **CNP**. Constitutive **GH** release from GH3 cells was greatly diminished in the presence of inhibitors for cAMP-dependent protein kinase, while stimulative **GH** release by **CNP** was not affected. However, inhibitors which can block cGK almost completely diminished the stimulative effect of **CNP**. An inhibitor for protein kinase C did not show any effect on either constitutive or **CNP** -stimulative **GH** release. Our observations indicate that the stimulation of **GH** release from GH3 cells by **CNP** is mediated mainly by the cGK signal-transduction pathway, not by cAMP-dependent protein kinase or protein kinase C, through a **CNP** -specific receptor (possibly ANP-B receptor). Thus, **CNP** may act as a local modulator in the anterior pituitary.

L5 ANSWER 16 OF 21 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 93309441 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8321215
TITLE: Cell-type-specific function of the **C-type natriuretic peptide** gene promoter in rat anterior pituitary-derived cultured cell lines.
AUTHOR: Ohta S; Shimekake Y; Nagata K
CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka 553, Japan.
SOURCE: Molecular and cellular biology, (1993 Jul) 13 (7) 4077-86. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930813
Last Updated on STN: 19990129
Entered Medline: 19930730

AB The promoter function of the human **C-type natriuretic peptide** (**CNP**) gene in various cultured cells was examined by transient transfection assays. The **CNP** promoter functioned very effectively in GH3 cells, which originated from the **growth hormone**-producing tumor of the rat anterior pituitary and somatomammotroph phenotype, but functioned much less effectively in GH1 cells, another type of rat pituitary-derived cell with a somatotroph phenotype, and rat primary cardiocytes. The **CNP** promoter did not function at all in other cells, including AtT20 cells of murine pituitary corticotroph origin. Functional analyses of the deleted promoters with various 5' deletion breakpoints revealed the existence of at least two negative and one positive regulatory regions. Within the positive regulatory region (positions -54 to -19), which conferred 90% of the promoter activity in GH3 cells, two equipotent GC-rich cis elements (positions -49 to -45 and -40 to -35) were

identified. Both sites shared half of the promoter activity and binding properties to the nuclear protein in GH3 cells. Rat anterior pituitary tissue contained the binding protein of the identified cis element, which was identical or similar to that of GH3 cells. With Southwestern (DNA-protein) analysis, a 70-kDa specific binding protein distinct from known factors such as SP-1, AP-2, and Pit-1 was identified in the nuclear extract of GH3 cells.

L5 ANSWER 17 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1993:318673 BIOSIS
DOCUMENT NUMBER: PREV199396027023
TITLE: Cyclic guanosine monophosphate production in the pituitary: Stimulation by **C-type natriuretic peptide** and inhibition by gonadotropin-releasing hormone in alpha-T3-1 cells.
AUTHOR(S): McArdle, Craig A. [Reprint author]; Poch, Annette; Kaeppler, Katrin
CORPORATE SOURCE: Inst. Hormone and Fertility Res., Univ. Hamburg, Grandweg 64, 2000 Hamburg 54, Germany
SOURCE: Endocrinology, (1993) Vol. 132, No. 5, pp. 2065-2072. CODEN: ENDOAO. ISSN: 0013-7227.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Jul 1993
Last Updated on STN: 3 Jan 1995

AB Atrial, brain-type, and **C-type natriuretic peptides** (ANP, BNP, and **CNP**) act via receptors with intrinsic guanylate cyclase activity. The A-type and B-type ANP receptors are selectively activated by ANP and **CNP**, respectively. The anterior pituitary is a site of ANP production and action, suggesting a local regulatory function, and this may also hold true for **CNP** which is found at its highest tissue concentrations in the anterior pituitary. Here we show that these peptides all cause dose-dependent increases in cGMP accumulation in alpha-T3-1 cells (a gonadotrope-derived cell line), **GH**-3 cells, and in primary cultures of rat pituitary cells. The response to **CNP** is particularly robust in alpha-T3-1 cells (59 +- 9-fold increase, EC-50 14 +- 3 nM), and the rank order of potency in alpha-T3-1 cells and primary cultures (**CNP** mchgt ANP gt BNP) is suggestive of action exerted via B-type receptors. Although **CNP** did not alter GnRH-stimulated LH release or (3H)inositol phosphate accumulation, GnRH reduced **CNP**-stimulated cGMP accumulation dose dependently (EC-50 apprx 0.1 nM). This inhibition reflects the ability of GnRH to shift the **CNP** dose-response curve rightward (increasing the EC-50 for **CNP** action approximately 10-fold both with and without 3-isobutyl-1-methylxanthine). The inhibitory effect was not blocked by omission of extracellular Ca++ nor mimicked by the Ca++ ionophore A23187 but was mimicked by a protein kinase C (PKC)-activating phorbol ester (which had a comparable effect to GnRH on the EC-50 for **CNP** action). The data imply that **CNP** rather than (or in addition to) ANP may have a local regulatory function within the pituitary, that although its role is currently unknown it may involve functional interaction with GnRH in gonadotropes, and that the effect of GnRH on **CNP** action may be PKC-mediated. Moreover, we suggest that alpha-T3-1 cells may be a useful model for investigation of the cross-talk between the B-type natriuretic peptide receptor-regulated signal transduction pathway and the Ca++/PKC pathway activated by ligand-stimulated hydrolysis of inositol phospholipids.

L5 ANSWER 18 OF 21 MEDLINE on STN DUPLICATE 8

ACCESSION NUMBER: 89055051 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3193044
TITLE: Effect of **growth hormone** on growth and

myelination in the neonatal hypothyroid rat.
AUTHOR: King R A; Smith R M; Meller D J; Dahlenburg G W; Lineham J D
CORPORATE SOURCE: CSIRO (Australia), Division of Human Nutrition, Adelaide, South Australia.
SOURCE: Journal of endocrinology, (1988 Oct) 119 (1) 117-25.
Journal code: 0375363. ISSN: 0022-0795.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198901
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19890106

AB The possible involvement of a deficit of **GH** and insulin-like growth factor-I (somatomedin C) (IGF-I/SMC) in mediating the effects of propylthiouracil (PTU)-induced hypothyroidism on body and skeletal growth and myelination was studied in the neonatal rat. Myelination (as assessed by 2',3'-cyclic nucleotide 3'-phosphohydrolase (**CNP**) activity), skeletal growth (as assessed by tail length) and body weight of pups from PTU-treated mothers were significantly retarded compared with normal animals or euthyroid controls. At 20 days after birth, plasma **GH** in hypothyroid animals was undetectable (less than 10 micrograms/l), pituitary **GH** content was 1.2% of control, and plasma, liver and kidney IGF-I/SMC concentrations were 63, 68 and 50% of control values respectively. **CNP** activity in hypothyroid brain was 52% of normal controls but the concentration of IGF-I/SMC was 113-154% of control. Treatment of hypothyroid animals from day 1 with **GH** (10 mg/kg body weight per day) restored liver and plasma IGF-I/SMC concentrations at 20 days to values above those of normal animals and euthyroid controls. The concentration of IGF-I/SMC was also significantly (P less than 0.001) restored in hypothyroid kidney (79% of normal), but the concentration in brain was unaffected. These observations provide evidence that the **GH** treatment employed in the present experiments was adequate to restore the deficit. **GH** treatment had no significant effect on tail length or **CNP** activity, and only a small (4-24%) effect on body weight at 20 days. Only thyroxine was able fully to restore body weight and substantially restore tail length and **CNP** activity.(ABSTRACT TRUNCATED AT 250 WORDS)

L5 ANSWER 19 OF 21 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 9
ACCESSION NUMBER: 85227946 EMBASE
DOCUMENT NUMBER: 1985227946
TITLE: Epidermal growth factor and bovine **growth hormone** stimulate differentiation and myelination of brain cell aggregates in culture.
AUTHOR: Almazan G.; Honegger P.; Matthieu J.-M.; Guentert-Lauber B.
CORPORATE SOURCE: Service de Pediatrie, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne, Switzerland
SOURCE: Developmental Brain Research, (1985) Vol. 21, No. 2, pp. 257-264. .
CODEN: DBRRDB
COUNTRY: Netherlands
DOCUMENT TYPE: Journal
FILE SEGMENT: 008 Neurology and Neurosurgery
002 Physiology
021 Developmental Biology and Teratology
003 Endocrinology
LANGUAGE: English
ENTRY DATE: Entered STN: 911210
Last Updated on STN: 911210

AB Bovine **growth hormone** (bGH) and epidermal growth

factor (EGF) increased the activity of ornithine decarboxylase (ODC) in brain cell aggregates cultured in a serum-free chemically defined medium. ODC is considered as a marker of cell growth and differentiation. The effect of bGH and EGF on myelination was investigated by measuring two myelin markers, 2',3'-cyclic nucleotide 3'-phosphodiesterase (**CNP** ) and myelin basic protein (MBP). EGF treatment at days 2 and 5 caused a dose-dependent increase of both myelin markers at culture day 12. This increase could still be observed at culture day 19, indicating a prolonged action of EGF. The continual presence of bGH in the culture medium produced a large accumulation of MBP at day 19. This effect was dose-dependent and required the presence of triiodothyronine (T3). In contrast, the effect of bGH on **CNP** activity did not require the presence of T3. This is the first report showing a direct effect of bGH on CNS myelination in vitro and of EGF on both MBP accumulation and ODC activity.

L5 ANSWER 20 OF 21 MEDLINE on STN
ACCESSION NUMBER: 86001732 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2412655
TITLE: Epidermal growth factor and bovine **growth hormone** stimulate differentiation and myelination of brain cell aggregates in culture.
AUTHOR: Almazan G; Honegger P; Matthieu J M; Guentert-Lauber B
SOURCE: Brain research, (1985 Aug) 353 (2) 257-64.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198510
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 20000303
Entered Medline: 19851029

AB Bovine **growth hormone** (bGH) and epidermal growth factor (EGF) increased the activity of ornithine decarboxylase (ODC) in brain cell aggregates cultured in a serum-free chemically defined medium. ODC is considered as a marker of cell growth and differentiation. The effect of bGH and EGF on myelination was investigated by measuring two myelin markers, 2',3'-cyclic nucleotide 3'-phosphodiesterase (**CNP** ) and myelin basic protein (MBP). EGF treatment at days 2 and 5 caused a dose-dependent increase of both myelin markers at culture day 12. This increase could still be observed at culture day 19, indicating a prolonged action of EGF. The continual presence of bGH in the culture medium produced a large accumulation of MBP at day 19. This effect was dose-dependent and required the presence of triiodothyronine (T3). In contrast, the effect of bGH on **CNP** activity did not require the presence of T3. This is the first report showing a direct effect of bGH on CNS myelination in vitro and of EGF on both MBP accumulation and ODC activity.

L5 ANSWER 21 OF 21 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 83163218 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6834036
TITLE: Cerebroside and sulfatide biosynthesis in the brain of Snell dwarf mouse: effects of thyroxine and **growth hormone** in the early postnatal period.
AUTHOR: Sarlieve L L; Bouchon R; Koehl C; Neskovic N M
SOURCE: Journal of neurochemistry, (1983 Apr) 40 (4) 1058-62.
Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198305

ENTRY DATE: Entered STN: 19900318
Last Updated on STN: 19990129
Entered Medline: 19830505

AB Snell dwarf mice (dw/dw) and normal mice (+/?) were injected with thyroxine (T4) (1 microgram/animal, four injections) and **growth hormone** (**GH**) (20 micrograms/animal, four injections) from the 5th to the 15th day of life. In the untreated dw/dw mouse brain, the specific activities of UDP-galactose:ceramide galactosyltransferase (CGalT), PAPS:cerebroside sulfotransferase (CST), and 2', 3'-cyclic nucleotide 3'-phosphohydrolase (**CNP**) were decreased by 28, 25, and 37%, respectively, compared with the control untreated +/? mice. The major effect of T4 was an increase of the brain **CNP** in the +/? mice (+40%) and dw/dw mice (+111%). The treatment with T4 also brought to normal the level of CGalT in dw/dw brain; a somewhat less marked effect on CST was observed. The treatment with **GH** had a great stimulatory effect on **CNP**: the specific activity of this enzyme increased by 40 and 69% in +/? and dw/dw mouse brain, respectively. On the contrary, no effect of **GH** on the CGalT activity was observed in this study. Our results suggest that T4 and **GH** may have both independent and complementary actions on the myelin-associated enzymes during the early postnatal period of brain development.

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